IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

DECLARATION UNDER 37 C.F.R. 1.132 Address to: Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Attorney Docket No.	CALD-005
	First Named Inventor	CALDWELL, LARRY
	Confirmation Number	3760
	Application Number	10/029,408
	Filing Date	December 26, 2001
	Group Art Unit	1618
	Examiner Name	OH, SIMON J.
	Title:	METHODS AND COMPOSITIONS FOR TREATING CARPAL TUNNEL SYNDROME

Dear Sir:

I, Bradley Galer, am an inventor of the subject matter claimed in the patent application identified above. Enclosed is a copy of my C.V. which demonstrates that I am qualified to speak on the level of one of skill in the art.

I hereby declare as follows:

1. I have read both the Advisory Action dated April 18, 2006 and the Office Action dated October 5, 2005 that issued in the above referenced case. I have also read Petrus (U.S. Patent No. 6,399,093), the reference cited in support of the rejections made by the Office.

2. Petrus characterizes musculoskeletal disorders as follows:

The musculoskeletal system consists of bones, muscles and joints. Ten percent of medical visits to physicians are for disorders of the musculoskeletal system. Musculoskeletal disorder include: sprains, strains, tendinitis, tenosynovitis, fibromyalgia, osteoarthritis, rheumatoid arthritis, gout, pseudogout (calcium pyrophosphate deposition disease), polymyalgia rheumatica, bursitis, acute and chronic back pain and osteoporosis, which interfere with the normal performance of activities of daily living. Injuries include sprains, strains and tears of ligaments, tendons, muscles and cartilage damage. Pain is the most common symptom and is frequently caused by injury or inflammation. Besides pain, other symptoms such as stiffness, tenderness, weakness and swelling or deformity of affected parts are manifestations of musculoskeletal disorders. Sports injuries are a significant cause of musculoskeletal disorders resulting in pain, strain, sprains, stiffness and leg cramps.

3. As can be seen with reference to the above, Petrus teaches that the musculoskeletal system consists of the bones, muscles and the joints. As such, the pain conditions which Petrus targets are conditions arising from trauma or dysfunction with the bones, muscles and joints without direct trauma or dysfunction within the peripheral nervous system. This can clearly be seen with reference to the working examples set forth in Petrus, which are directed to the treatment of gout, osteoarthritis and rheumatoid arthritis. As can be seen with reference to Exhibit A, Petrus's teaching is consistent with how gout, osteoarthritis and rheumatoid arthritis are characterized and classified by the International Association for the Study of Pain, the world's leading medical and scientific society on pain. See for example, Exhibit A, page 126, which characterizes Osteoarthritis of the Hands (page 48) as arising from the musculoskeletal system, Rheumatoid arthritis (page 47) as arising from the musculoskeletal system and connective tissue, and Gout as arising from (page 49-50) inflammation of the joint, and therefore the musculoskeletal system. Accordingly, as viewed in the light of Exhibit A all of these specific conditions, set forth in Petrus, have a musculoskeletal origin.

4. In contrast, Carpal Tunnel Syndrome is not a species of musculoskeletal disorders. Rather, Carpal Tunnel Syndrome is a condition whose symptoms are caused by a disturbance of median nerve function in the wrist as the nerve passes through the carpal tunnel. As such, the pain caused by Carpal Tunnel Syndrome does not arise from the musculoskeletal system. Instead, the pain, parasthesia, and dysesthesia arise from direct trauma and dysfunction to the median nerve within the carpal tunnel. In fact, the International Association for the Study of Pain defines and classifies Carpal Tunnel Syndrome as arising from the peripheral nervous system, and not the musculoskeletal system. See Exhibit B, page 127. Accordingly, as viewed in the light of Exhibit B Carpal Tunnel Syndrome is not a musculoskeletal disorder, rather it is a neurological disorder that results from an entrapment neuropathy.

5. Therefore, based on my review of Petrus and in light of Exhibits A and B, it is my opinion that one of skill in the art would understand Petrus to be directed to the treatment of musculoskeletal disorders and that musculoskeletal disorders do not include Carpal Tunnel Syndrome. One of skill in the art would understand that musculoskeletal disorders do not include Carpal Tunnel Syndrome because the symptoms of Carpal Tunnel Syndrome arise from a completely different system and is categorized differently by the IASP.

6. Accordingly, in view of the difference in classification of musculoskeletal disorders and Carpal Tunnel Syndrome, those of skill in the art would approach the treatment of neuropathic pain conditions, of which Carpal Tunnel Syndrome is a member, differently from how they would approach the treatment of musculoskeletal pain disorders. In general, different classes of medications are prescribed for the treatment of neuropathic pain conditions as compared to the treatment of musculoskeletal pain disorders. See for example Exhibits C and D.

a. Exhibit C is an excerpt from an article entitled: Algorithm for Neuropathic Pain Treatment: An Evidence Based Proposal. The article sets forth a comparison of the various treatments used in the amelioration of neuropathic

pains. Among the treatments used to remedy neuropathic pains are antidepressants (section 3.2) and anticonvulsants (section 3.3). See Finnerup, N. B. Pain 2005; 118:289-305 at page 290.

b. Exhibit D is an excerpt from the book entitled: Evidenced-Based Management of Acute Musculoskeletal Pain. The excerpt sets forth various treatments recommended for the management of acute musculoskeletal pains. The excerpt specifically points out that there is no evidence that supports the use of anti-depressants or anticonvulsants in the treatment of acute musculoskeletal pain. See page 22.

c. Accordingly, as can be seen with reference to Exhibits C and D, one of skill in the art would approach the treatment of a neuropathic pain differently from how they would approach the treatment of a musculoskeletal pain because in the treatment of a neuropathic pain one of skill in the art may recommend the administration of an anti-depressant or anticonvulsant where as for the treatment of a musculoskeletal pain one would not recommend the administration of an anti-depressant or anticonvulsant.

7. As such, Petrus does not teach one of skill in the art anything about the treatment of neuropathic pain conditions such as Carpal Tunnel Syndrome.

I hereby declare that all statements made herein are of my own knowledge and are true, and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patents issued there from.

Respectfully submitted,

Date: 6/2/05 By: _____

Bradley Galer

enc:

- CV of Bradley Galer
- Exhibit A-Classification of Chronic Pain, pages 47, 48 and 49
- Exhibit B-Classification of Chronic Pain, page 127
- Exhibit C- Finnerup, N. B. Pain. 2005; 118:289-305, page 290
- Exhibit D- Evidenced-Based Management of Acute Musculoskeletal Pain, page 22

Bradley Stuart Galer, M.D.

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West Chester, PA 19382
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Personal Data

Date of Birth:	July 21, 1961
Place of Birth:	Boston, Massachusetts
Family:	Wife - Anna
	Children - Alexander, Peter, & Simon

Education

Albert Einstein College of Medicine, 1983-1987
Bronx, New York
Degree: M.D., June 1987

Wesleyan University, 1979-1983
Middletown, Connecticut
Degree: B.A., Biology-Psychology, June 1983

Postgraduate Training

Internship:	Kaiser Foundation Hospital, 1987-1988 Oakland, California
Residency:	Albert Einstein Neurology Residency Program, 1988-1991 Bronx, New York
Chief Resident:	Albert Einstein Neurology Residency Program, 1990-1991 Bronx, New York
Headache Training	Montefiore Headache Clinic, 1990-1991 Bronx, New York
Headache Training	University of California San Francisco, 1992 San Francisco, CA
Pain Fellowship:	Memorial Sloane-Kettering Cancer Center, 1990-1991 (4 months) New York, New York (Drs. Kathleen Foley and Russell Portenoy)
Pain Fellowship:	University of California San Francisco, 1991-1992 San Francisco, CA (Drs. Howard Fields and Michael Rowbotham)
Business School	Wharton Executive Education, 2002; Business Leadership Training
	Harvard Business School Executive Education, 2005 Leadership & Strategy in Pharmaceutical and Biotech

Industry Positions

TOPICEUTICAL INC
- Chairman of the Board, CEO, President. October 2005 - present

ENDO PHARMACEUTICALS INC
- Group Vice President, Scientific Affairs & Senior Medical. August 2003- September 2005.
- Vice President, Scientific Affairs & Senior Medical Officer. August 2000- August 2003

CALDWELL-GALER INC
- Co-Founder, Chairman of the Board. September 1997 – November 2005

Other Industry Experience

- 1992-98, co-lead investigator and co-developer clinical development plan for Lidoderm
- 1998, originator and lead coordinator of Endo's licensing Lidoderm from Hind Health Care

Industry Roles & Responsibilities

ENDO (2000- present)
- Reported directly to Executive Vice President
- Direct reports included Clinical Research, Clinical Operations, Medical Affairs, Safety Pharmacoviligance and Risk Management, Clinical Development and Education, Pharmacoeconomics
- Provide clinical and scientific leadership for the development and marketing of analgesic products
- Design clinical development plans and protocols for registration and market support (Phase I-IV)
- Assist in regulatory strategy
- Writing and editing of clinical study reports
- Writing and editing of NDA
- Lead cross-functional project teams in the execution of phase I-IV clinical trials ensuring successful studies in accordance with GCP/ICH guidelines
- Interpret clinical data
- Directly interface with FDA
- Direct scientific dissemination of data via publications and presentations
- Lead Endo medical/clinical representative to press
- Clinical and scientific lead in business development with assessment of licensing opportunities
- Lead Medical Liaison Group with Thought Leader development and all educational initiatives
- Reviewed all clinical sections of regulatory documents including study reports, INDs, NDAs, annual reports, Investigator Brochures and labeling
- Prepare annual budgets for Scientific Affairs (up to $25 million)

Drug Development Experience

Lidoderm®	1991-1999	Regulatory strategy, Phase 3 study design/execution (Hind Health Care, Consultant)
	2000-2005	Life Cycle Management (LCM) strategy/execution (Endo)
Oxymorphone ER/IR	2000-2005	Phase 1-3 regulator strategy, study design/execution, NDA preparation (Endo)
Oxydone ER generic	2000-2004	Clinical review of Paragraph 4, development of Risk Management Program (Endo)
DepoDur®	2003-2005	NDA preparation, LCM (Endo)
Percocet®	2000-2005	LCM (Endo)
MorphiDex®	2000-2003	Regulatory strategy, Phase 3 study design/execution (Endo)
Neurontin	1995-2000	Phase 3 study design, LCM (Parke-Davis, Pfizer, Consultant)
Lyrica	1998-2000	Phase 3 study design/execution (Pfizer, Consultant)
Effexor	1995-1997	Phase 3 study design/execution (Wyeth, Consultant)
Tizanidine	1998-2000	LCM (Elan, Consultant)
ABT-484	1995-1998	Phase 2 POC study design (Abbott, Consultant)
GV196771	1998-2000	Phase 2 POC study design/execution (Glaxo Wellcome, Consultant)
Topical Clonidine	1996-2000	Regulatory Strategy, Phase 2/3 study design (Curatek, Lead Consultant)

Faculty Positions Held

Acting Assistant Professor of Anesthesia/Adjunct Assistant Professor of Neurology
University of Washington School of Medicine
Seattle, Washington
1992- 1994

Assistant Professor of Anesthesia/Adjunct Assistant Professor of Neurology
University of Washington School of Medicine
Seattle, Washington
1994 – April 1996

Assistant Professor of Neurology/Adjunct Asst. Professor of Anesthesiology
Washington School of Medicine
Seattle, Washington
May 1996 - May 1998

Associate Professor of Neurology
Albert Einstein College of Medicine
Bronx, NY
1999-2000

Faculty Positions Held (cont'd)

Adjunct Assistant Professor of Neurology (Associated Faculty)
University of Pennsylvania School of Medicine
Philadelphia, Pennsylvania
October 2001 – October 2004

University of Washington Medical Center Positions Held (1993 - May 1998)

Attending, Multidisciplinary Pain Center
Director, Pain Clinical Research Center
Medical Director, Headache Program
Medical Director, Reflex Sympathetic Dystrophy Program

Beth Israel Medical Center Positions Held (May 1998 – August 2000)

Attending, Pain Division of the Department of Pain Medicine & Palliative Care
Attending, Department of Neurology
Director of Clinical Studies, Institute for Education and Research
in Pain & Palliative Care
Co-Director, Nerve Pain Disorders Clinic

Board Certification

American Academy of Pain Management, November 1, 1996 {Certificate # 6712}

Honors

Keeney Scholarship, for Achievement in Academics and Community Involvement
Wesleyan University, 1981-1983

Phi Beta Kappa
Wesleyan University, 1982-1983

Doyle Award, Medical Student with Highest Achievement in Neurology
Medical Degree with Special Distinction in Clinical Neurology Research (Pain)
Albert Einstein College of Medicine, 1987

Young Investigator Travel Award, American Pain Society, 1991

"Best Doctors in America: Pacific Region, 1996-1997;1998-1999, Neurology
(Pain Management)

"Best Doctors in America," 1998 (entire USA, Pain Management/Neurology)

"Tele Award," (for best medical documentary, cable TV)- Co-write and Co-host,
"Understanding Shingles", 2000

Honors (Cont'd)

First "Annual Neuropathy Organization Honoree," (for work in neuropathic pain), New York City, 2004

Academic Memberships

International Association for the Study of Pain (IASP)
Neuropathic Pain, Sympathetic Nervous System and RSD/CRPS Special Interest Group (IASP)
International Headache Society
American Headache Society
American Pain Society
American Academy of Pain Medicine
American Academy of Pain Management
American Association for the Study of Headache
American Academy of Neurology
Reflex Sympathetic Dystrophy Syndrome Association
Phi Beta Kappa

Academic Administrative Duties

Reflex Sympathetic Dystrophy Program, University of Washington, 1993 - May 1998; develop comprehensive multidisciplinary outpatient program, (physicians, psychology, physical therapy, occupational therapy, vocational counselor, and nursing)

Pain Clinical Research Center, University of Washington, 1992 - May 1998; Founder; obtain, protocol development, perform, and supervise pain clinical research staff, (pharmaceutical industry clinical trials and other clinical research activities); 3 research coordinators and 3 research assistants

Director of Clinical Studies, Institute for Education and Research in Pain & Palliative Care, Beth Israel Medical Center, May 1998 – 2000

Group Vice President, Scientific Affairs. Endo Pharmaceuticals Inc. Supervise 45 persons. Responsible for Clinical Operations, Clinical Research, Medical Affairs, and Clinical Development & Education. August 2000- present. Active in clinical trial design, portfolio strategy, pharmacovigilance and safety, publication planning, educational course development, business development and marketing strategy.

Special Responsibilities – Elected Boards, Editorialships and Journal Reviewer

Scientific Advisory Board, NeurAxon (2006-*present*)
Editorial Advisory Board, *Current Drug Therapy* (2005-*present*)
Director at Large (elected), Eastern Pain Association (2002- *present*)
Board of Directors, Reflex Sympathetic Dystrophy Syndrome Association (2002- *present*)
Founding Editor and Editor, *Current Pain and Headache Reports(1999 – present)*
Editorial Board, *The Clinical Journal of Pain (2000 - present)*

Special Responsibilities – Elected Boards, Editorialships and Journal Reviewer (cont'd)

Associate Editor, *The Clinical Journal of Pain (1998 - 2000)*
Editorial Board, *Journal of Back and Musculoskeletal Rehabilitation*
Editor, *Progress in Pain for Primary Care (1999-2000)*
Book Editor, *Journal of Pain and Symptom Management (1998-2000)*
Series Editor, *Progress in Pain for Primary Care*
Supplement Editor, *Neurology Reviews Supplement: Management of Neuropathic Pain*
Supplement Editor, *The Clinical Journal of Pain: International Conference of Neuropathic Pain*
Expert Analyst Editor, *The Pain Medicine Journal Club Journal*
Ad Hoc Reviewer, *JAMA*
Ad Hoc Reviewer, *Pain*
Ad Hoc Reviewer, *American Family Physician*
Ad Hoc Reviewer, *Journal of General Internal Medicine*
Ad Hoc Reviewer, *Journal of Pain and Symptom Management*
Ad Hoc Reviewer, *Pharmacoeconomics*

Other Responsibilities

Invited Member, IMMPACT (Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials), closed round-table with FDA, Academia, NIH, and Industry, 2002- present
Invited Member, Promoting the Health of People with Disabilities (CDC)-Diabetes Task Force, 1992, 1993
Consultant, Quality of Life in Migraine Study-University of Washington Department of Health Services Cost and Outcome Assessment Team, 1993
Medical Student Research Training Program Advisor, 1993
Consultant, Cost and Effectiveness of Care for Chronic Conditions-Center for Health Studies, 1994
Education Committee- American Academy of Pain Medicine, 1995-96
Invited author, presenter, participant - 1995
USA Congressional NIH Report-Chronic Pain and Peripheral Neuropathies
Advisor, American Board of Pain Medicine- Certification Examination, 1997
Pain Medicine Section of American Academy of Neurology
Founding Member and Executive Committee, 1995- present
Vice-Chairman, Chairman elect - 1996-97
Co-Chairman, Education Committee, 1995 - present,
Chairman, 1998-2000
Chairman of Professional Development Courses. American Pain Society's 18th Annual Conference, 1998-1999.
Panel member, Cancer Pain Management Guideline Panel, Clinical Practice Guidelines Program, American Pain Society, 1999

Founder, National Director, National Conferences on Pain Management for the Primary Care Physician (American Pain Society), 1998-2001
Co-Chairman / Steering Committee, Annual International Neuropathic Pain Conference, 1998-present

Other Responsibilities (cont'd)

Workshop Organizer and Moderator, IASP 9th World Congress on Pain,
"Prognostic Utility of Intravenous Infusion Treatment of Neuropathic Pain: Lidocaine, Opioid, and Phentolamine," 1999
IASP 2nd Annual Research Symposium- Founder and co-chair, "CRPS." Wales, UK. 2000
Key role in establishment of Endo sponsored "Essentials of Pain Management Program for Residents," 2002 - present

Invited Advisory Panels/Boards/Consultation

Chair and Moderator, National Drug Advisory Board Meeting, Parke-Davis, 2000
Advisory Boards:
Pfizer
Merck Research
Abbott Laboratories
Roche Bioscience
Watson Pharmaceutical
Consultant, Elan Pharmaceutical
Consultant, GlaxoWellcome
Emerging Concepts of Anticonvulsants for Chronic Pain – 1996
Consultant, Myelos Neurosciences- 1998

National Guidelines for Neuropathic Pain Treatment for the Primary Care Physician - 1997
National Guidelines for Pain Management in Long-Term Nursing Facilities - 1997, 1998
Management of Pain, Myofascial Pain Syndromes - 1998
Participant, International Neuropathic Pain Treatment Guideline Consensus Meeting- 2001

Invited Non-Profit Organizations Board Membership

Reflex Sympathetic Dystrophy Syndrome Association- 2002-present

Patents- Issued (USA)

1. Method for Treating Headache Pain with Topical Local Anesthetic Compositions
Inventor: CALDWELL LARRY; GALER BRADLEY STUART
Assignee: TOPICEUTICAL INC

2. Method for Treating Neuroma Pain
Inventor: GALER BS; CALDWELL J
Assignee: CALDWELL GALER INC

Patent Applications (publicly disclosed)

1. Methods and compositions for treating headache pain with topical NSAID compositions
Inventor: CALDWELL LARRY; GALER BRADLEY STUART
Assignee: TOPICEUTICAL INC

Patent Applications (publicly disclosed)

2. Methods for treating indomethacin responsive headaches
   Inventor: GALER BRADLEY S; NEWMAN LAWRENCE
   Assignee: TOPICEUTICAL INC

3. Methods and compositions for treating carpal tunnel syndrome (topical NSAID)
   Inventor: CALDWELL LARRY; GALER BRADLEY STUART
   Assignee: CALDWELL GALER INC

4. Compositions and methods for treating neuropathic sensory loss
   Inventor: GALER BRADLEY S
   Assignee: ENDO PHARMACEUTICALS INC

5. Abuse-resistant opioid dosage formulations
   Inventor: GALER BRADLEY; KAO HUAIHUNG D
   Assignee: ENDO PHARMACEUTICALS INC

6. Method for deterring abuse of opioids by combination of non-release formulation of emetic
   Inventor: GALER BRADLEY STUART; GAMMAITONI ARNOLD
   Assignee: ENDO PHARMACEUTICALS INC

7. Method for treating non-neuropathic pain
   Inventor: STUART GALER BRADLEY
   Assignee: ENDO PHARMACEUTICALS INC

8. Composition and method for treating neuropathic sensory loss.
   Inventor: DWORKIN ROBERT D; GALER BRADLEY STUART
   Assignee: ENDO PHARMACEUTICALS INC

9. Abuse resistant pharmaceutical composition containing capsaicin
   Inventor: GOLDBERG M; GALER B S
   Assignee: ENDO PHARMACEUTICALS INC

10. Abuse-resistant opioid solid dosage form
    Inventor: KAO HUAIHUNG; GALER BRADLEY
    Assignee: ENDO PHARMACEUTICALS INC

11. Pharmaceutical composition and method for treating disorders of central nervous system.
    Inventor: GALER BRADLEY S; SCHLAGHECK THOMAS G
    Assignee: ENDO PHARMACEUTICALS INC

11. Abuse resistant pharmaceutical composition containing capsaicin
    Inventor: GOLDBERG MICHAEL; GALER BRADLEY STUART
    Assignee: ENDO PHARMACEUTICALS INC

Businesses

Topiceutical Inc. Founder, CEO, President. 2005 – present.
Development and commercialization of topical drugs for the treatment of pain and headache.

Caldwell Galer, Inc. (CGI) Co-Founder & Chairman of the Board. 1997 – present
Development of topical drugs for the treatment of pain and headache.

Academic Funded Grants

1993-1995, Principal investigator - "Multicenter randomized, double-blind study of the analgesic efficacy during 30 days of as needed use of topical lidocaine patches and lidocaine gel in patients with postherpetic neuralgia". Private funding: Hind Health Care, Inc.

1996-1998, Principal Investigator- "Multicenter randomized, double-blind study of the analgesic efficacy of topical lidocaine patches and lidocaine gel in patients with painful diabetic neuropathy." Private funding: Hind Health Care, Inc. /Teikoku Seiyaku Co., Ltd.

1996-1997, Principal Investigator- "Multicenter randomized, double-blind study of the analgesic efficacy of topical diclofenac patches in the treatment of acute minor sports injury pain." Private funding: Institut Biochimique SA/Teikoku Seiyaku Co., Ltd.

1996-1998, Investigator- "Multicenter randomized, double-blind study of the analgesic efficacy of venlafaxine-ER in patients with postherpetic neuralgia." Private funding: Wyeth-Ayerst Research.

1996-1998, Principal Investigator- "Double-blind, randomized, placebo-controlled, cross-over study to determine the efficacy and safety of Rilutek in subjects with peripheral neuropathic pain." Private funding: Rhone-Poulenc Rorer Pharmaceuticals.

1997-1998, Principal Investigator, "Comparision study of the analgesic efficacy and safety of transdermal versus topical clonidine gel in patients with postherpetic neuralgia." Private funding: Curatek Pharmaceuticals.

1997, Investigator- "A randomized, double-blind, placebo-controlled, two period crossover study to explore the preliminary safety, tolerability, and efficacy of oral L-754,030 in the treatment of postherpetic neuralgia." Private funding: Merck Research Laboratories.

1997-1998, Principal Investigator, "Open label pilot study of the analgesic efficacy and safety of topical clonidine in patients with reflex sympathetic dystrophy (complex regional pain syndrome)." Private funding: Curatek Pharmaceuticals.

1997-1998, Principal Investigator, "Enriched enrollment, double-blind, cross-over design study of the analgesic efficacy of topical lidocaine patches in patients with postherpetic neuralgia". Private funding: Hind Health Care, Inc.

Academic Funded Grants (cont'd)

1997 - 1998, Sole Investigator, "Pain Medicine Survey of 700 Practicing Neurologists and Neurology Residency Program Directors in America," in conjuction with the American Academy of Neurology.

1998-1999, Co-Investigator, "A Double-blind Placebo-Controlled Trial of Pregabalin for Treatment of Painful Diabetic Peripheral Neuropathy." Private funding: Parke-Davis Pharmaceutical Research.

1998-1999, Co-Investigator. "Pregabalin Open-label Follow-On Safety Trial in Patients With Painful Diabetic Peripheral Neuropathy." Private funding: Parke-Davis Pharmaceutical Research.

1998-1999, Principal Investigator. "A Double-blind Placebo-Controlled Trial of Pregabalin for Treatment of Postherpetic Neuralgia." Private funding: Parke-Davis Pharmaceutical Research.

1998-1999, Co-Investigator. "Pregabalin Open-label Follow-On Safety Trial in Patients With Postherpetic Neuralgia." Private funding: Parke-Davis Pharmaceutical Research.

1998-1999. Principal Investigator. "A Pilot, Multicenter, Double-Blind, Placebo Controlled, Randomized, Cross-Over Study to Evaluate the Efficacy, Safety, and Tolerability of Remacemide Hydrochloride 600mg/day in Subjects with Moderate to Severe Neuropathic Pain." Private funding: Astra Pharmaceutical Research.

1998-1999. Principal Investigator. "A Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel Group Evaluation of a 14 Day Course of 300mg of GV196771 in Subjects with Chronic Neuropathic Pain." Private funding: Glaxo-Wellcome Research.

1998-1999, Co-Investigator. "A Repeated-dose Evaluation of Analgesic Use and Safety of Dilaudid SR (Hydromorphone HCL) in Patients with Chronic Cancer Pain." Private funding: Knoll Pharmaceutical.

1998-1999, Co-Investigator. "A Randomized, Double-blind, Placebo-controlled Eficacy, Safety and Outcomes Trial of Controlled Release-Oxycodone (Oxycontin) in Painful Diabetic Polyneuropathy." Private funding: Purdue Pharma LP.

1999, Principal Investigator- "Multicenter randomized, double-blind study of the analgesic efficacy of topical diclofenac patches in the treatment of acute minor sports injury pain." Private funding: Institut Biochimique SA.

Invited Papers, Lectures, Presentations - Neuropathic Pain

University of Washington Multidisciplinary Pain Center Grand Rounds- 1991, 1992, 1993,1994, 1995,1996, 1997
University of Washington Neurology Grand Rounds- 1992, 1993, 1996, 1998
University of Washington Geriatric Grand Rounds- 1992
University of Washington Neurological Surgery Grand Rounds- 1992

Invited Papers, Lectures, Presentations - Neuropathic Pain (cont'd)

University of Washington Treatment of Hand Problems, CME course-1994
University of Washington Physical Medicine and Rehabilitation Grand Rounds- 1995
University of Washington Pain CME Course- 1994, 1996
University of Washington Physical Medicine and Rehabilitation CME Course- 1996
University of Oregon Health Sciences, Rheumatology Update, Bend, Oregon- 1993
Saint Joseph Hospital, Internal Medicine Grand Rounds, Spokane, WA- 1993
Dannemiller Foundation, Pain Treatment for the Neurologist, New York- 1993
Bremerton Naval Base Hospital, Family Medicine Grand Rounds, Bremerton, WA-1993
Congress of Neurological Surgeons 43rd Annual Meeting, Vancouver, B.C.- 1993
Northwest Regional Conference for Occupational/Physical Therapy, Bellevue,WA- 1993
Kaiser Permanente Hospital, Medicine Grand Rounds, Los Angeles, CA-1994
Kaiser Permanente Hospital, Medicine Grand Rounds, Montabello, CA-1994
Group Health Cooperative, Medicine Grand Rounds, Redmond, WA-1994
Providence Hospital, Medicine Grand Rounds, Yakima, WA-1994
International Society of Critical Care Conference, San Francisco, CA- 1995
Valley Medical Center, Pain Management Course, Renton, WA- 1995
Maricopa Medical Center, Medical Grand Rounds, Phoenix, AZ- 1995
Los Angeles Neurological Society, Grand Rounds, Los Angeles, CA- 1995
Chronic Pain and Pain Mechanisms, San Franscisco, CA- 1995
American Pain Society, Los Angeles, CA- 1995
NIH Workshop on Selected Chronic Pain Conditions, Bethesda, MD- 1995
Emerging Applications for Anticonvulsants in the Management of Pain- Dallas,1996
Parke-Davis Neurology Consultants Meeting, Aspen, CO-1996
Eastern Washington State Hospital, Spokane, WA- 1996
Spokane Neurology Group, Spokane, WA- 1996
Emerging Applications for Anticonvulsants in the Management of Pain-audioconfmce,1996
Emerging Applications for Anticonvulsants in the Management of Pain- Honolulu, HY; Seattle, WA; Tacoma, WA; Bellevue, WA; Spokane,WA;
Newport Beach, CA 1996
Private Practice Neurologists, Internists - Seattle, WA 1996
St. John Medical Center - Longview, WA 1996
Madigan Army Medical Center- Tacoma, WA 1996
Spokane Primary Care Physicians- Spokane, WA 1996
Coere d'Elane Generalists- Coeur d'Alene, ID 1996
Internal Medicine Review Course, Tacoma, WA 1997
American Academy of Neurology- Boston, MA 1997
Hawaii (7 lectures to primary care physicians/neurologists) - 1997
Emerging Concepts of Antiepileptic Drugs- San Diego CA, Los Angeles CA,
Las Vegas NV, Seattle WA, Pasadena CA, Snowbird Utah- 1997
Chronic Pain Management - Swedish Medical Center, Seattle WA - 1997
American Pain Society- New Orleans 1997
Private Practice Neurologists - Everett, WA 1997
Neurological Nurses Association of Washington, Seattle, WA 1998
North Shore Medical Center, Neurology Grand Rounds, Manhasset, NY. July 1998
Private Practice Physicians- Seattle, WA September 1998
Neurological Institute, Columbia School of Medicine,New York, NY 1999
Hannahman School of Medicine, Philadelphia, PA 1999

Invited Papers, Lectures, Presentations - Neuropathic Pain (cont'd)

Vanderbilt School of Medine, Nashville, TN 1999
2nd World Congress in Neurological Rehabilitation, Toronto, Canada, 1999
Neurogenic Pain, Pavia Italy, 1999
Neurology Grand Rounds, University of Rome Italy, 1999
International Neuropathic Pain Conference- Washington, DC, 1999
Japan Society of Drug Delivery Systems- Takamatsu, Kagawa Japan, 1999
Osaka Pain Group- Osaka Japan, 1999
International Association for the Study of Pain 9th World Congress on Pain (2 lectures and moderator), Vienna Austria, 1999
University of Washington Neurology Grand Rounds, Seattle WA 2001
University of Washington Pain Grand Rounds, Seattle WA 2001
Washington State Annual DO Conference, Blaine WA 2001
Georgetown Pain Grand Rounds, Washington DC 2001
University of Utah, Annual Pain Conference, Snowbird UT 2002
American Academy of Pain Management Nurses, Salt LakeCity UT 2002
United Kingdom Pain Society- Plenary Lecture, Bournemouth UK 2002
Harvard Medical School Pain Course- Boston MA 2005

Invited Papers, Lectures, Presentations - RSD (Complex Regional Pain Syndromes)

University of Washington Multidisciplinary Pain Center Grand Rounds- 1991, 1992, 1993,1994, 1995,1996, 1997
University of Washington Neurology Grand Rounds, 1996
Los Angeles Neurological Society, Los Angeles, CA- 1995
NIH Workshop on Selected Chronic Pain Conditions, Bethesda, MD- 1995
Emerging Applications for Anticonvulsants in Pain, workshop leader, Dallas, TX- 1996
Chronic Pain Symposium, North Shore Medical Center, NY- 1996
American Pain Society, Washington, D.C.- 1996
International Meeting on Neuropathic Pain, Rochester, NY. June 1998
Hannahman School of Medicine, Philadelphia, PA 1999
Beth Israel Medical Center Neurology Grand Rounds, New York NY 1999
IASP Research Conference, Wales UK 2000
International Update on RSD/CRPS , Tampa FLA 2002
Eastern Pain Society, NY, NY 2002

Invited Papers, Lectures, Presentations - Analgesic Clinical Trial Design & Pain Measurement
International Neuropathic Pain Conference, Washington DC, 2000
American Academy of Neurology, Philadelphia PA 2001
Residents Program, American Pain Society, Baltimore MD 2002
American Academy of Neurology, Denver CO 2002
World Congress of Pain, San Diego CA 2002
International Neuropathic Pain Conference, Bermuda 2002
Harvard Pain Course, Boston, 2005

Invited Papers, Lectures, Presentations - Headache

Medex, Physicians Assistant Program- 1993
Multidisciplinary Pain Center Grand Rounds- 1994, 1995, 1996
Office Management of Chronic Pain, CME course- 1994
Neurology Grand Rounds- 1994, 1996
Family Medicing Grand Rounds- 1994
General Lecture to Public, University of Washington Medical Center- 1996
Barnes & Nobles- Bellvue WA- 1997
University of Oregon Health Sciences, Rheumatology Update, Bend, Oregon- 1993
Sacred Heart Hospital, Medicine Grand Rounds, Spokane, WA- 1993
Bend Memorial Clinic, Family Medicine Grand Rounds, Bend, Oregon- 1993
Portland Emergency Room Staff, Portland, Oregon- 1993
Northwest Regional Conference for Occupational/Physical Therapy, Bellevue,WA- 1993
Valley General Hospital, Renton, WA- 1994
Kaiser Permanente Hospital, Portland, WA- 1994(2)
Billings Community Hospital, Billings, MT- 1994
Rose Medical Center, Medicine Grand Rounds, Denver, CO- 1994
Benefits Expo (Health Care Managers), Minneapolis-1994
Group Health Cooperative, Silverdale, WA - 1995
Kaiser Permanente Hospital, Los Angeles, CA - 1995,1996
Kaiser Permanente Hospital, Portand, Oregon - 1995

Public Media

Endo Public Medical Spokesperson- 2000-2005.

Television host and writer- "Understanding Shingles". The Health Network, 1999-2000, ½ hour television show for consumers.

Medical Chat Room Expert- Pain Management. Yahoo/The Health Network, 2000.

Medical Writer, "Pain" and "What's New in Pain", www.stoppain.org, 1998-2000.

Course Development

Faculty, Presenter, Workshop Leader- Curriculum Development for CME Course on "Emerging Applications for Anticonvulsants in Pain," Profession Postgraduate Services, Dallas, TX- March, 1996

Co-Chair, American Pain Society 1996 Annual Meeting- Clinical Symposium, "CRPS-I (RSD)- Primarily a Disuse/Neglect-like Phenomenon Requiring Primarily a Rehabilitation Approach?", Washington, DC- October 1996

Moderator, American Pain Society 1996 Annual Meeting- Clinical Symposium, "'Psychogenic Pain'- Harmful to our Patients' Health", New Orleans, LA- October 1997

Course Development (con'td)

Workshop leader, Moderator, 1999 International Association for the Study of Pain, 9th World Congress of Pain - "Diagnostic, Therapeutic, and Prognostic Uses of Intravenous Infusions in Chronic Pain Syndromes," Vienna Austria, August 1999

Chair, Program Development Courses, 1999 American Pain Society Meeting, Fort Lauderdale, Fla.

Program Development Courses, 2000 American Pain Society Meeting, Atlanta, Ga.

Chair, Program Developer, American Pain Society's National Pain Management Course for the Primary Care Physician, 1999, New York.

Co-Chair, International Neuropathic Pain Conference, 1999, Washington, DC.

Co-Chair, International Neuropathic Pain Conference, 2000, Washington, DC.

Organizing Committee, International Association for the Study of Pain Research Symposium: Complex Regional Pain Syndrome, 2000, U.K.

Co-Chair, International Neuropathic Pain Conference, 2001, San Francisco CA

Steering Committe, International Neuropathic Pain Conference, 2002, Bermuda

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1. Sinnamon HS, **Galer BS**. Head Movements Elicited by Electrical Stimulation of the Anteromedial Cortex of the Rat. *Physiol & Behav* 1984;33:185-190.

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4. **Galer BS**, Lipton RB, Weinstein S, Bello L, Solomon S. Apoplectic Headache and Oculomotor Nerve Palsy: An Unusual Presentation of Multiple Sclerosis. *Neurology* 1990;40:1465-1466.

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5. **Galer BS**, Lipton RB, Kaplan R, Kaplan JG, Arezzo JC, Portenoy RK. Bilateral Burning Foot Pain: Monitering of Pain, Sensation and Autonomic Function During Successful Treatment with Sympathetic Blockade. *J Pain Symptom Manage* 1990;6:92-97.

6. Lipton RB, **Galer BS**, Dutcher JP, Portenoy RK, Pahmer V, Meller F, Arezzo JC, Wiernik PH. Large and Small Fibre Type Sensory Dysfunction in Patients with Cancer. *J Neurol Neurosurg Psychiatry* 1991;54:706-709.

7. **Galer BS**, Lipton RB, Solomon S, Newman LC, Spierings ELH. Myocardial Ischemia Related to Ergot Alkaloids: A Case Report and Literature Review. *Headache* 1991;31:446-450.

8. **Galer BS**, Coyle N, Pasternak GW, Portenoy RK. Individual Variability in the Response to Different Opioids: report of five Cases. *Pain* 1992;49:87-91.

9. **Galer BS**, Rowbotham MC, Fields HL. Treatment of Inflammatory, Neuropathic and Sympathetically Mediated Pain in a patient with Sjogren's Syndrome. *Pain* 1992;50:205-208.

10. **Galer BS**, Miller KV, Rowbotham MC. Response to Intravenous Lidocaine Infusion Differs Based Clinical Diagnosis and Site of Nervous System Injury. *Neurology* 1993;43:1233-1235.

11. Fitzgibbon D, **Galer BS**. Efficacy of Opiates in Cancer Pain. *Pain* 1994;58:429-31.

12. **Galer BS**, Butler S, Jensen M. Case Reports and Hypothesis: A Neglect-like Syndrome may be responsible for the Motor Disturbance in Reflex Sympathetic Dystrophy. *J Pain Sympt Management* 1995;10:385-392.

13. Von Korff M, **Galer BS**, Stang PE. Chronic Use of Symptomatic Headache Medication in Primary Care. *Pain* 1995;62:179-186.

14. **Galer BS**. Preliminary Report: Peak Pain Relief is Delayed and Duration of Relief is Extended following Intravenous Phentolamine Infusion. *Reg Anesth* 1995;20:444-447.

15. Rowbotham MC, Davies PJ, Verkempinck CM, **Galer BS**. Lidocaine Patch: Double-blind Controlled Study of A New Treatment Method for Postherpetic Neuralgia. *Pain* 1996;65:39-45.

16. **Galer BS**, Harle, J, Rowbotham MC. Response to Intravenous Lidocaine Infusion Predicts Subsequent Response to Oral Mexiletine: A Prospective Study. *J Pain Symptom Management* 1996;12:161-167.

Original Publications (cont'd)

17. Wagner TH, Patrick DL, **Galer BS**, Berzon R. A New Quality-of-Life Measure for Migraine, the MSQOL: Development and Psychometric Testing. *Headache* 1996;36:484-492.

18. **Galer BS**, Jensen M. Development and Preliminary Validation of a Pain Measure Specific to Neuropathic Pain: The Neuropathic Pain Scale. *Neurology* 1997;48:332-339.

19. **Galer BS**, Schwartz L, Turner J. Do Patient and Physician Expectations Predict Pain Relief? *Clin J Pain* 1997;13:348-351.

20. **Galer BS**, Bruehl S, Harden RN. IASP Diagnostic Criteria for Complex Regional Pain Syndrome (CRPS): a preliminary empirical validation study. *Clin J Pain* 1998;14:48-54.

21. Stang P, Von Korff M, **Galer BS**. Reduced Labor Force Participation Among Primary Care Headache Patients. *Journal of General Internal Medicine* 1998;13:296-302.

23. Carter G, Jensen M, **Galer BS**, Kraft G, Crabtree L, Beardsley RM, Abresch R, Bird, T. Pain in Charcot-Marie-Tooth Disease. *Arch of Phys Med and Rehab* 1998;79:1560-1564.

24. Shibata M, Nakao K, **Galer BS**, Shimzu T, Taniguchi H, Uchida T. A Case of RSD (CRPS I) Resolved by Cerebral Contusion. *Pain*, 1999;79:313-315.

25. **Galer BS**, Rowbotham MC, Perander J, Friedman E. Topical Lidocaine patch Relieves Postherpetic Neuralgia more effectively than a vehicle topical patch: Results of an Enriched Enrollment Study. *Pain,* 1999;80:533-538.

26. Allan G, **Galer BS**, Schwartz L. Epidemiological Review of 134 Patients with Complex Regional Pain Syndrome Assessed in a Chronic Pain Clinic. *Pain*, 1999;80:539-544.

27. Harden N, Bruehl S, **Galer BS**, Salz S, Bertram M, Backonja M, Gayles, R, Stanton-Hicks M, Rudin. External Validition of IASP Diagnostic Criteria for Complex Regional Pain Syndrome and Proposed Research Diagnostic Criteria. *Pain*, 1999;81:147-155.

28. Rashiq S, **Galer BS**. Myofascial Dysfunction in Complex Regional Pain Syndrome. *Clin J Pain* 1999;15:151-153.

29. Black L, Saunders K, Von Korff M, **Galer BS**. Headache Medication Use Among Primary Care Headache Patients in a Health Maintenance Organization. *Cephalalgia*, 1999;19:575-580.

30. **Galer BS**, Jensen M. Neglect-like Symptoms in Complex Regional Pain Syndrome: Results of a Self-administered Survey. *J Pain and Sympt Manage* 1999;18:213-217.

31. **Galer BS**, Keran C, Frisinger, M. Pain Medicine Education Among American Neurologists: A Need for Improvement. *Neurology* 1999;52:1710-1712.

Original Publications (cont'd)

32. Harden N, Bruehl S, **Galer BS**, Salz S, Bertram M, Backonja M, Gayles, R, Stanton-Hicks M, Rudin. Complex Regional Pain Syndrome: Are the IASP Diagnostic Criteria Valid and Sufficiently Comprehensive? *Pain* 1999;83:211-221.

33. **Galer BS**, Friedman E, Perander J, Devers A, Ford G, Quiring J, Rowbotham M. Topical Diclofenac Patch Relieves Acute Minor Sports Injury Pain: Results of a Controlled Clinical Trial. *J Pain and Sympt Manage,* 2000;19:287-294.

34. **Galer BS**, Gianas A, Jensen. Painful Diabetic Polyneuropathy: Epidemiology, Pain Description, and Quality of Life. *Diabetes Research and Clinical Practice,* 2000;47:123-128.

35. **Galer BS**. Advances in the Treatment of Postherpetic Neuralgia: The Topical Lidocaine Patch. *Today's Therapeutic Trends,* 2000;18:1-20.

36. Cramer GW, **Galer BS**, Mendelson MA, Thompson GD.. A Drug Use Evaluation of Selected Opioids and Nonopioid Analgesics in Nursing Facilities. *J Am Geriat Soc,* 2000;48:398-404.

37. Devers A, **Galer BS**, Topical Lidocaine Patch Relieves a Variety of Neuropathic Pain Conditons: An Open Label Pilot Study. *Clin J Pain*, 2000;16:205-208.

38. **Galer BS**, Jensen M. Complex Regional Pain Syndrome: Epidemiology, Pain Description, and Quality of Life. *J Pain Symptom Manage*, 2000;20:236-292.

39. **Galer BS**, Twilling LL, Harle J, Cluff, R, Friedman E, Rowbotham MC. Lack of Efficacy of Riluzole in the Treatment of Neuropathic Pain Conditions. *Neurology*, 2000;55;971-975.

40. Gabb MG and **Galer BS**. A closer look at the tools used to diagnosis and assess neuropathic pain. *Advanced Studies in Medicine,* 2001;1:248-254.

41. **Galer BS**, Jensen M, Ma T, Davies PS, Rowbotham MC. The Lidocaine 5% Patch Effectively Treats All Neuropathic Pain Qualities: Results of a Randomized Vehicle-Controlled, Double-blind Study Using the Neuropathic Pain Scale. *Clin J Pain*, 2002;18:297-301.

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45. Gammaitoni AR, **Galer BS**, Bulloch S, Lacouture P, Caruso F, Ma T, Schlagheck T. Randomized, Double-Blind, Placebo-Controlled Comparison of the Analgesic Efficacy of Oxycodone 10 mg/Acetaminophen 325 mg vs Controlled-Release Oxycodone 20 mg in Postsurgical Pain. *J Clin Pharmacol*, 2003;43:296-304.

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50. Dworkin RH, Backonja M, Rowbotham MC, Allen RR, Argoff CR, Bennett GJ, Bushnell C, Farrar JT, **Galer BS**, Haythornthwaite JA, Hewitt DJ, Loeser JD, Max MB, Saltarelli M, Schmader KE, Stein C, Thompson D, Turk DC, Wallace MS, Watkins LR, Weinstein SM. Advances in neuropathic pain: diagnosis, mechanisms, and treatment recommendations. *Archives of Neurology*, 2003;60: 1524-1534.

51. Turk DC, Dworkin RH, Allen RR, Bellamy N, Brandenburg N, Carr DB, Cleeland C, Dionne R, Farrar JT, **Galer BS**, Hewitt DJ, Jadad AR, Katz NP, Kramer LD, Manning DC, McCormick CG, McDermott MP, McGrath P, Quessy S, Rappaport BA, Robinson JP, Royal MA, Simon L, Stauffer JW, Stein W, Tollett J, Witter J. Core outcome domains for chronic pain clinical trials: IMMPACT recommendations. *Pain*. 2003;106(3):337-45.

52. Davies PD and **Galer BS**. Review of Lidocaine Patch 5% Studies in the Treatment of Postherpetic Neuralgia. *DRUGS*, 2004;64(9):937-947.

53. **Galer BS**, Sheldon E, Patel N, Codding C, Burch F, Gammaitoni A. Topical Lidocaine Patch 5% may target a novel underlying pain mechanism in osteoarthritis. *Current Medical Research and Opinion*, 2004;20(9):1455-1458.

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55. Jensen MP, Dworkin RH, Gammaitoni AR, Olaleye DO, Oleka N, **Galer BS**. Assessment of pain quality in chronic neuropathic and nociceptive pain clinical trials with the Neuropathic Pain Scale. *J Pain*. 2005;6(2):98-106.

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1. **Galer, BS.** Chronic Pain and Headache- An Interactive Learning Program for Patients, Primary Care Physicians, Nurses, Physician Assistants, and Medical Students [CD-ROM], Hoffman & Associates, 2001.

Books

1. **Galer, BS** and Dworkin, R. A Clinical Guide to Neuropathic Pain, McGaw-Hill Publishers, 2000.

Invited Review Articles / Book Chapters

1. **Galer BS**, Portenoy RK. Acute Herpetic Neuralgia and Postherpetic Neuralgia: Clinical Features and Management. *Mt Sinai J Med* 58:257-266;1991.

2. Bowdle TA, **Galer BS**. Agonist-antagonist and Partial Agonist Opioids: Pharmacology Medhanisms and Clinical Application in the Treatment of Headache. *Headache Quarterly*, 4:322-36, 1993.

3. **Galer BS**. Painful Polyneuropathy: Diagnosis, Pathophysiology, and Treatment. *Sem Neurol*, 14:237-246, 1994.

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4. **Galer BS**. Neuropathic Pain of Peripheral Origin-Advances in Pharmacologic Treatment. *Neurology*, 45(Suppl 9):S17-S25, 1995.

5. **Galer BS**, Loeser JD, Von Korff M. Painful Diabetic Neuropathy. NIH Report on Chronic Pain. 1995.

6. **Galer BS**, Loeser JD, Von Korff M. Reflex Sympathetic Dystrophy (Complex Regional Pain Syndrome, Type 1). NIH Report on Chronic Pain. 1995.

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8. Loeser JD, **Galer BS**, Von Korff M. Postherpetic Neuralgia. NIH Report on Chronic Pain. 1995

9. **Galer BS**, Argoff C. Zoster and Postherpetic Neuralgia: Pain Mechanisms and Current Management [book chapter]. In: Aronoff, G: *Evaluation and Treatment of Chronic Pain*. Williams & Wilkens, 1998.

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16. Carter GT and **Galer BS**. Advances in the Treatment of Neuropathic Pain. In: Carter GT: *Physical Medicine and Rehabilitation Clinics of North America*. May WB Saunders Inc, 2001.

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Invited Commentaries/ Editorials

1. **Galer BS**. Opioids and Chronic Nonmalignant Pain. *APS Journal* 2:207;1993.

2. **Galer BS**. Diabetic Neuropathy. *American Pain Society Bulletin* 3:18;1993.

3. **Galer BS**. Commentary on Sumitriptan and Headache. *APC Journal Club* 1993.

4. **Galer BS**. Commentary on Carpal Tunnel Syndrome. *Pain Med J Club* 1(2):72-73,1995.

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5. Dworkin RH, **Galer BS**, Rowbotham MC. Herpes Zoster. *New Engl J Med.* 2000;343:221-222.

6. **Galer BS.** Response to: Response to letter regarding 'impaired self-perception of the hand in complex regional pain syndrome.' *Pain*, 117: 242.

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1. **Galer, BS.** American Pain Society J. Review of Olesen, J and Schoenen, J (eds): *Frontiers in Headache Research, Vol 3, Tension-Type Headache*. Raven Press, 1994.

2. **Galer, BS.** American Pain Society J. Review of Olesen, J, Tfelt-Hansen, P, and Welch, KMA (eds): *The Headaches*. Raven Press, 1994. Summer 1994, p 144.

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5. **Galer, BS**. Annals of Neurology. Review of Portenoy, RK and Kanner, RM (eds): *Pain Management: Theory and Practice- Contempory Neurology Series (Vol 48).* F. A. Davis, 1996. 40(4);1996:123.

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1. Portenoy RK, **Galer BS**, Salomon O, Freilich M, Berger M, Finkel JE, Lipton RB, Milstein D. Identification of Epidural Neoplasm: Radiography and Bone Scintigraphy in the Symptomatic and Asymptomatic Spine. *Neurology* 38 (Suppl 1):210;1988. Presented at the 40th Annual Meeting of the Academy of Neurology, 1988.

2. Lipton RB, **Galer BS**, Dutcher JP, Meller F, Pahmer V, Arezzo JC, Wiernik PH, Schaumburg HH. Large and Small Fiber Type Sensory Dysfunction in Patients with Cancer. *Neurology* 39(Suppl1):320;1989. Presented at the 41st Annual Meeting of the Academy of Neurology, 1989.

3. Breitbart W, Portenoy RK, **Galer BS**, Passik S. Pain in the Ambulatory AIDS Patient: Prevalence and Psychosocial Correlates. Presented at the 38th Annual Meeting of Psychosomatic Medicine, 1991.

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4. **Galer BS**, Miller KV, Rowbotham MC. Response to Intravenous Lidocaine Infusion Differs Based on CNS or PNS origin of Neuropathic Pain. *Neurology* 42 (Suppl 3):391,1992. Presented at the 44th Annual Meeting of the Academy of Neurology, 1992.

5. Rowbotham MC, **Galer BS**, Allen RR, Davies PJ, Verkempinck CM, Keller LR. Lidocaine Patch for Postherpetic Neuralgia: Results of a Double-blind Placebo Controlled Trial. Presented at the 7th World Congress of Pain, Paris, France, 1993.

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8. **Galer BS**, Kitahara M. Intramuscular Stimulation for the Treatment of Chronic Headache. American Association for the Study of Headache, June 1995.

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14. **Galer BS**, Keran C, Frisinger, M. Pain Medicine Education Among American Neurologists: A Need for Improvement. American Academy of Neurology, April 1999, Toronto Canada.

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16. **Galer BS**, Twilling LL, Harle J, Cluff, R, Rowbotham MC. Efficacy of Riluzole in the Treatment of Neuropathic Pain Conditions. American Pain Society, October 1999, Fort Lauderdale Florida.

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18. Lidocaine Patch 5% Treats All Neuropathic Pain Qualities: Results of a Randomized Clinical Trial Using the Neuropathic Pain Scale. American Academy of Pain Medicine. February 2002.

19. Lidocaine Patch 5% Treats All Neuropathic Pain Qualities: Results of a Randomized Clinical Trial Using the Neuropathic Pain Scale. American Academy of Neurology. April 2002.

20. Lidocaine Patch 5% Treats All Neuropathic Pain Qualities: Results of a Randomized Clinical Trial Using the Neuropathic Pain Scale. American Society of Regional Anesthesia. April 2002.

21. OPEN-LABEL STUDY OF THE EFFECTIVENESS AND SAFETY OF LIDOCAINE PATCH 5% (LIDODERM) IN PATIENTS WITH PAINFUL DIABETIC NEUROPATHY. World Congress on Pain. August 2002.

22. EFFECTIVENESS OF LIDOCAINE PATCH 5% ON VARIOUS PAIN QUALITIES ASSOCIATED WITH DIABETIC NEUROPATHY: A PROSPECTIVE TRIAL USING THE NEUROPATHIC PAIN SCALE. World Congress on Pain. August 2002.

23. Assessment of Opioid-Sparing and Tolerance in Chronic Non-Malignant Pain Patients with the NMDA-Enhanced Analgesic EN3231: Results of a 3-month randomized, controlled trial World Congress on Pain. August 2002.

24. Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Single-Dose Study of Oxycodone 10 mg/Acetaminophen 325 mg vs Oxycodone 20 mg Alone in Patients With Acute Pain Following Third Molar Extraction. American Association of Oral and Maxillofacial Surgeons (AAOMS). October 2002.

Abstracts (abbreviated- stopped listing after 2002)

25. FIXED TID DOSING OF NEW FORMULATIONS OF OXYCODONE/ACETAMINOPHEN SIGNIFICANTLY REDUCES PAIN INTENSITY AND PAIN INTERFERENCE WITH QUALITY OF LIFE IN PATIENTS WITH CHRONIC LOW BACK PAIN. American Osteopathic Association. October 2002.

26. Efficacy and safety of EN3231, an NMDA-enhanced analgesic: results of a 3-month randomized controlled trial demonstrate faster resolution of opioid related side effects compared to morphine alone. American Society of Regional Anesthesia and Pain Medicine (ASRA). November 2002.

27. EN3231, AN NMDA-ENHANCED ANALGESIC, PROVIDES COMPARABLE ANALGESIA WITH A 50% REDUCTION IN OPIOID DOSE VS MORPHINE ALONE IN ARTHRITIS PATIENTS. American Society of Regional Anesthesiology. November 2002.

28. Effectiveness and Safety of the Lidocaine Patch 5% as Add-On Treatment to Gabapentin in Patients With Postherpetic Neuralgia, Diabetic Neuropathy, or Low Back Pain: Results of a Prospective, Open-Label, Multicenter Study. American Society of Consultant Pharmacists. November 2002.

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Abstracts (abbreviated- stopped listing after 2002)

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35. IMPACT OF LIDOCAINE PATCH 5% ON PAIN INTENSITY AND PAIN RELIEF WHEN USED IN COMBINATION WITH GABAPENTIN IN 3 CHRONIC PAIN STATES. 5th International Neuropathic Pain Meeting. November 2002

36. EVALUATION OF THE IMPACT OF THE LIDOCAINE PATCH 5% ON QUALITY OF LIFE IN PATIENTS WITH PAIN FROM OSTEOARTHRITIS. American Society of Hospital Pharmacist . December 2002.

37. LIDOCAINE PATCH 5% IMPROVES PAIN INTENSITY AND PAIN RELIEF WHEN USED IN COMBINATION WITH GABAPENTIN IN 3 CHRONIC NEUROPATHIC PAIN STATES. American Society of Hospital Pharmacist . December 2002.

38. A PROSPECTIVE, MULTICENTER, OPEN LABEL TRIAL OF THE LIDOCAINE PATCH 5% IN PAINFUL DIABETIC NEUROPATHY. American Society of Hospital Pharmacist . December 2002.

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EXHIBIT A

CLASSIFICATION OF CHRONIC PAIN

DESCRIPTIONS OF CHRONIC PAIN SYNDROMES AND DEFINITIONS OF PAIN TERMS

Second Edition

prepared by the

Task Force on Taxonomy
of the
International Association for the Study of Pain

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2. Simultaneous soft tissue swelling or fluid in at least three joint areas observed by a physician. The 14 possible areas are right or left proximal interphalangeal joints (PIP), metacarpal phalangeal (MCP), wrist, elbow, knee, ankle, and metatarsal phalangeal joints (MTP).
3. At least one area of soft tissue swelling or effusion in a wrist, MCP, or PIP joint.
4. Symmetrical arthritis. Simultaneous involvement of the same joint areas as defined in 2 above in both sides of the body (bilateral involvement of PIP, MCP, or MTP is acceptable without absolute symmetry).
5. Rheumatoid nodules.
6. Positive serum rheumatoid factor, demonstrable by any method for which any result has been positive in less than 5% of normal control subjects.
7. Radiographic changes typical of rheumatoid arthritis on posterior-anterior hand and wrist radiographs; this must include erosions or unequivocal bony decalcification which is periarticular.

A patient fulfilling four of these seven criteria can be said to have rheumatoid arthritis. Criteria 1–4 must have been present for at least six weeks.

Differential Diagnosis
Systemic lupus erythematosus, palindromic rheumatism, mixed connective tissue disease, psoriatic arthropathy, calcium pyrophosphate deposition disease, seronegative spondyloarthropathies, hemochromatosis (rarely).

Code
X34.X3a

Reference
Arnett, F.C., Edworthy, S.M., Bloch, D.A., et al., The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis, Arthritis Rheum., 31 (1988) 315–324.

Osteoarthritis (I-11)

Definition
Deep, aching pain due to a "degenerative" process in a single joint or multiple joints, either as a primary phenomenon or secondary to other disease.

Site
Joints most commonly involved are distal and proximal interphalangeal joints of the hands, the carpo-metacarpal thumb joint, the knees, the hips, and cervical and lumbar spines. Many joints or only a few joints may be affected, e.g., at C5 or L5, the hip or knee; proximal joints may be involved alone or only distal interphalangeal joints.

System
Musculoskeletal system.

Main Features
There is deep, aching pain which may be severe as the disease progresses. The pain is felt at the joint or joints involved but may be referred to adjacent muscle groups. Usually the pain increases in proportion to the amount of use of the joint. As the disease progresses there is pain at rest and later nocturnal pain. The pain tends to become more continuous as the severity of the process increases. Stiffness occurs after protracted periods of inactivity and in the morning but lasts less than half an hour as a rule.

There is a discrepancy between radiological prevalence and clinical complaints. Radiological evidence of osteoarthritis occurs in 80% of individuals over 55 years of age. Only about 25% of those with radiographic changes report symptoms. The incidence increases with age. There is a greater prevalence relatively in men under the age of 45 compared with women, and in women over the age of 45 compared with men.

Aggravating Features
Use, fatigue.

Signs
Clinically, joint line tenderness may be found and crepitus on active or passive joint motion; noninflammatory effusions are common. Later stage disease is accompanied by gross deformity, bony-hypertrophy, contracture. X-ray evidence of joint space narrowing, sclerosis, cysts, and osteophytes may occur.

Laboratory Findings
None specific.

Usual Course
Initially there is pain with use and minimal X-ray and clinical findings. Later pain becomes more prolonged as the disease progresses and nocturnal pain occurs. The course is one of gradually progressive pain and deformity.

Relief
Some have relief with nonsteroidal anti-inflammatory agents or with non-narcotic analgesics. Joint rest in the early stages relieves the pain. Occasional relief in the early phases may appear from intra-articular steroids.

Physical Disability
Progressive limitation of ambulation occurs in large weight-bearing joints.

Pathology
This is loosely described as a "degenerative" disease of articular cartilage.

Essential Features
Deep, aching pain associated with the characteristic "degenerative" changes in joints.

For classification purposes, patients will be said to have fibromyalgia if both criteria are satisfied. Widespread pain must have been present for at least three months. The presence of a second clinical disorder does not exclude the diagnosis of fibromyalgia.

Code
X33.X8a

References
Wolfe, F., Smythe, H.A., Yunus, M.B., et al., The American College of Rheumatology 1990 criteria for the classification of fibromyalgia: report of the Multicenter Criteria Committee, Arthritis Rheum., 33 (1990) 160–172.

Bennett, R.M. and Goldenberg, D.L. (Eds.), The fibromyalgia syndrome, Rheumatic Disease Clinics of North America, vol. 15, no. 1, WB Saunders, Philadelphia, 1989.

Note: Specific Myofascial Pain Syndromes

Synonyms: fibrositis (syndrome), myalgia, muscular rheumatism, nonarticular rheumatism.

Specific myofascial syndromes may occur in any voluntary muscle with referred pain, local and referred tenderness, and a tense shortened muscle. The pain has the same qualities as that of the diffuse syndromes. Passive stretch or strong voluntary contraction in the shortened position of the muscle is painful. Satellite tender points may develop within the area of pain reference of the initial trigger point. Other phenomena resemble those of the diffuse syndromes. Diagnosis depends upon the demonstration of a trigger point (tender point) and reproduction of the pain by maneuvers which place stress upon proximal structures or nerve roots. This suggests that the syndrome is an epiphenomenon secondary to proximal pathology such as nerve root irritation. Relief may be obtained by stretch and spray techniques, tender point compression, or tender point injection including the use of "dry" needling.

Some individual syndromes are described here, e.g., sternocleidomastoid and trapezius. Others may be coded as required according to individual muscles that are identified as being a site of trouble.

Rheumatoid Arthritis (I-10)

Definition
Aching, burning joint pain due to systemic inflammatory disease affecting all synovial joints, muscle, ligaments, and tendons in accordance with diagnostic criteria below.

Site
Symmetrical involvement of small and large joints

System
Musculoskeletal system and connective tissue

Main Features
Diffuse aching, burning pain in joints, usually moderately severe; usually intermittent with exacerbations and remissions. The condition affects about 1% of the population and is more common in women. Diagnostic criteria of the American Rheumatism Association describe and further define the illness. They are as follows: (1) morning stiffness, (2) pain on motion or tenderness at one joint or more, (3) swelling of one joint, (4) swelling of at least one other joint, and (5) symmetrical joint swelling.

All of the above have to be of at least six weeks duration. Further criteria include: (6) subcutaneous nodules, (7) typical radiographic changes, (8) positive test for rheumatoid factor in the serum, (9) a poor response in the mucin clot test in the synovial fluid, (10) synovial histopathology consistent with rheumatoid arthritis, and (11) characteristic nodule pathology.

Classical rheumatoid arthritis requires seven criteria to be diagnosed. Definite rheumatoid arthritis may be diagnosed on five criteria, and probable rheumatoid arthritis on three criteria.

Associated Symptoms
Morning stiffness usually greater than half an hour's duration; chronic fatigue. Inflammation may affect eyes, heart, lungs.

Signs
Tenderness, swelling, loss of range of motion of joints, ligaments, tendons. Chronic destruction and joint deformity are common.

Laboratory Findings
Anemia, raised ESR (erythrocyte sedimentation rate), rheumatoid factor in the serum in the majority of cases.

Relief
Usually good relief of pain and stiffness can be obtained with nonsteroidal anti-inflammatory drugs, but some patients require therapy with gold or other agents.

Pathology
Chronic inflammatory process of synovium, ligaments, or tendons. There may be systemic vasculitis.

Essential Features
Aching, burning joint pain with characteristic pathology.

Diagnostic Criteria
1. Morning stiffness in and around joints lasting at least one hour before maximal improvement.

Diagnostic Criteria
No official diagnostic criteria exist for osteoarthritis, although criteria have been proposed for osteoarthritis of the knee joint.

Noninflammatory arthritis of one or several diarthrodial joints, occurring in the absence of any known predisposing cause, with loss of cartilage and/or bony sclerosis (or osteophyte formation) demonstrable by X-rays.

Differential Diagnosis
Calcium pyrophosphate deposition disease; presence of congenital traumatic, inflammatory, endocrinological, or metabolic disease to which the osteoarthritis may be secondary.

Code
X38.X6a

Calcium Pyrophosphate Dihydrate Deposition Disease (CPPD) (I-12)

Definition
Attacks of aching, sharp, and throbbing pain with acute or chronic recurrent inflammation of a joint caused by calcium pyrophosphate crystals.

Site
Usually one joint, sometimes more, often alternating. Knees, wrists, and metacarpo-phalangeal joints are most frequent sites.

System
Musculoskeletal system.

Main Features
The disorder occurs clinically in about 1 in 1000 adults, more often in the elderly, but radiology shows the presence of the disease in 5% of adults at the time of death. There are four major clinical presentations: (1) *pseudogout:* acute redness, heat, swelling, and severe pain which is aching, sharp, or throbbing in one or a few joints; the attacks last from 2 days to several weeks, with freedom from pain between attacks; (2) *pseudorheumatoid arthritis:* marked by deep aching and swelling in multiple joints, with attacks lasting weeks to months; (3) *pseudo-osteoarthritis*: see the description of osteoarthritic features; and (4) *pseudarthritis with acute attacks*: the pain being the same as in osteoarthritis but with superimposed acute painful swollen joints.

Signs
Aspiration of calcium pyrophosphate crystals from the joint is diagnostic. X-rays show calcification in the cartilage of the wrists, knees, and symphysis pubis.

Relief
Acute attacks respond well to nonsteroidal anti-inflammatory drugs, with or without local corticosteroid injections.

Complications
Chronic disabling arthritis.

Associated Disorders
Hyperparathyroidism, hemochromatosis. There may be hereditary, sporadic, or metabolic causes.

Pathology
Acute and chronic inflammation or degeneration.

Diagnostic Criteria
1. Demonstration of CPPD crystals in tissues or synovial fluid by definitive means such as X-ray diffraction.
2. Crystals compatible with CPPD demonstrable by compensated polarized light microscopy.
3. Typical calcifications seen on roentgenograms.

A definite diagnosis can be made if 1 above is present, or if 2 and 3 are present. A probable diagnosis can be made if 2 or 3 is present.

Differential Diagnosis
Gout, infection, palindromic rheumatism, osteoarthritis.

Code
X38.X0 or X38.X5a

Reference
Ryan, L.M. and McCarty, D.J., Calcium pyrophosphate crystal deposition disease: pseudogout articular chondrocalcinosis. In: D.J. McCarty (Ed.), Arthritis and Allied Conditions, 10th ed., Lea & Febiger, Philadelphia, 1985, pp. 1515–1546.

Gout (I-13)

Definition
Paroxysmal attacks of aching, sharp, or throbbing pain, usually severe and due to inflammation of a joint caused by monosodium urate crystals.

Site
First metatarso-phalangeal joints, midtarsal joints, ankles, knees, wrists, fingers, or elbows.

Main Features
More common in men in the fourth to sixth decades of life and in postmenopausal women. Acute severe paroxysmal attacks of pain occur with redness, heat, swelling, and tenderness, usually in one joint. The pain is aching, sharp, and throbbing. The patient is often unable to accept the weight of bedclothes on the joint and unable to

EXHIBIT B

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Signs
Bony enlargements of the distal interphalangeal joints are called Heberden's nodes, and those of the proximal interphalangeal joints are called Bouchard's nodes. The fingers may be stiff and lose some degree of full flexion. Grip strength is usually normal when measured.

Radiologic Finding
Narrowing of joint spaces, sclerosis, and bony osteophytosis.

Relief
Analgesics, soaking in hot fluids.

Code
238.X6b

Cubital Tunnel Syndrome (XI-15)

Definition
Entrapment of the ulnar nerve in a fibro-osseous tunnel formed by a groove (trochlear groove) between the olecranon process and medial epicondyle of the humerus. The groove is converted to a tunnel by a myofascial covering, and the etiology of the entrapment is multiple.

Site
Elbow, forearm, and fingers (fourth and fifth).

System
Peripheral nervous system (ulnar nerve).

Main Features
Gradual onset of pain, numbness, and paresthesias in the distribution of the ulnar nerve, sometimes followed by weakness and atrophy in the same distribution; often seen in conjunction with a carpal tunnel syndrome ("double crush phenomenon").

Signs and Laboratory Findings
Tinel's sign at the elbow. The ulnar nerve is frequently thickened and adherent. On electrodiagnostic testing there is slowing of conduction in the ulnar nerve across the elbow, accompanied by denervation of those intrinsic muscles of the hand innervated by the ulnar nerve.

Usual Course
The course may be stable or slowly progressive; if the latter, surgery is necessary, either decompression or transposition of the nerve.

Summary of Essential Features and Diagnostic Criteria
A gradual onset of pain, paresthesias, and, at times, motor findings in the distribution of the ulnar nerve. Tinel's sign is found. The diagnosis is confirmed by slowing of conduction across the elbow and often by denervation of those intrinsic muscles of the hand innervated by the ulnar nerve.

Differential Diagnosis
Thoracic outlet syndrome, carpal tunnel syndrome.

Code
202.X6c

Carpal Tunnel Syndrome (XI-16)

Definition
Stinging, burning, or aching pain in the hand, often nocturnal, due to entrapment of the median nerve in the carpal tunnel.

Site
One hand (sometimes bilateral), in the fingers, often including the fifth digit, often spreading into the forearm and occasionally higher; not usually well localized.

System
Peripheral nervous system.

Main Features
Prevalence: very common. *Age of Onset:* usually fourth to fifth decades. *Sex Ratio:* female to male 5:1. *Quality:* pins and needles, stinging, often aching, occasionally burning. *Time pattern:* usually nocturnal, typically awakening the patient several times and then subsiding in a few minutes; aching pain is often more constant. *Intensity:* may be severe briefly.

Associated Symptom
Aggravated by handwork such as knitting.

Signs and Laboratory Findings
Clinical examination often normal, but one may find decreased pin-prick sensation on the tips of digits I–III, a positive Tinel's or Phalen's sign, or rarely, weakness and/or atrophy of the thenar muscles (abductor pollicis brevis); nerve conduction studies showing delayed sensory and motor conduction across the carpal tunnel are diagnostic.

Usual Course
Very slow progression for years.

Social and Physical Disability
May impair ability to do handwork.

Pathology
Compression of median nerve in wrist between the carpal bones and the transverse carpal ligament (flexor retinaculum); focal demyelination of nerve fibers, axonal shrinkage and axonal degeneration.

EXHIBIT C

PAIN

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Research papers

Algorithm for neuropathic pain treatment: An evidence based proposal

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Abstract

New studies of the treatment of neuropathic pain have increased the need for an updated review of randomized, double-blind, placebo-controlled trials to support an evidence based algorithm to treat neuropathic pain conditions. Available studies were identified using a MEDLINE and EMBASE search. One hundred and five studies were included. Numbers needed to treat (NNT) and numbers needed to harm (NNH) were used to compare efficacy and safety of the treatments in different neuropathic pain syndromes. The quality of each trial was assessed. Tricyclic antidepressants and the anticonvulsants gabapentin and pregabalin were the most frequently studied drug classes. In peripheral neuropathic pain, the lowest NNT was for tricyclic antidepressants, followed by opioids and the anticonvulsants gabapentin and pregabalin. For central neuropathic pain there is limited data. NNT and NNH are currently the best way to assess relative efficacy and safety, but the need for dichotomous data, which may have to be estimated retrospectively for old trials, and the methodological complexity of pooling data from small cross-over and large parallel group trials, remain as limitations.

Keywords: Neuropathic pain; Pharmacological treatment; Algorithm; Number needed to treat

1. Introduction

Neuropathic pains are characterized by partial or complete somatosensory change in the innervation territory corresponding to peripheral or central nervous system pathology, and the paradoxical occurrence of pain and hypersensitivity phenomena within the denervated zone and its surroundings (Jensen et al., 2001). These sensory phenomena are seen across aetiologically different conditions and across different locations of the nerve lesion. Rarely, if ever, can one single mechanism be claimed responsible for generating and maintaining the symptoms and signs seen in neuropathic pain (Jensen and Baron, 2003; Woolf, 2004). Treatment of neuropathic pain is still difficult despite new treatments, and there is no single treatment that works for all conditions and their underlying mechanisms. Given the increasing evidence for effective treatments of neuropathic pain, it is important for the clinician to know which drugs are most effective in relieving pain and associated with the fewest adverse effects, and there is a need for an evidence-based algorithm to treat neuropathic pain conditions.

Ideally, the evidence for the drug choices in such an algorithm would be based on direct comparisons of one drug with another, for both efficacy and side effects. There are very few such direct comparisons available. An alternative approach is to estimate relative efficacy and safety using number needed to treat (NNT) and number needed to harm (NNH). Recent systematic reviews have summarized the available treatments for neuropathic pain using NNT values (McQuay et al., 1995; Sindrup and Jensen, 1999, 2000).

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However, these reviews need to be updated because of the publication of new trials, and the limitations of the NNT and NNH approach need to be discussed. This paper provides up-to-date calculations of NNT and NNH in neuropathic pain as the basis of a proposal for an evidence-based treatment algorithm.

2. Methods

2.1. Search strategy

Full reports of randomized placebo-controlled double-blind studies published in peer-reviewed journals were identified using free-text searches of MEDLINE (1966–April 2005), EMBASE (1974–April 2005), Cochrane Review, and Cochrane CENTRAL. Each drug was only searched by one author. Additional papers were identified from previous published reviews and reference lists of retrieved papers. Letters were sent to corresponding authors of papers that did not provide dichotomous data to ask if they could provide us with such data.

2.2. Selection criteria

Randomized double-blind studies in neuropathic pain conditions using chronic dosing and placebo studying at least 10 patients were included. Studies not written in English were excluded. Studies on cancer neuropathic pain were also excluded except for well-defined post-mastectomy pain syndromes and post-surgical pain with post-operative pain compatible with a nerve section.

2.3. Data abstraction, quality assessment, and quantitative data synthesis

From each study we extracted information on study design, inclusion and exclusion criteria, number of participants, drug dose, randomization and blinding procedure, description of dropouts, change in primary outcome measure, and pain relief during active and placebo treatment.

Number needed to treat was the principal effect measure. NNT is defined as the number of patients needed to treat with a certain drug to obtain one patient with a defined degree of pain relief, in the present context 50% pain relief, and is calculated as the reciprocal of the absolute risk difference (Cook and Sackett, 1995; McQuay et al., 1996). If 50% pain relief could not be obtained directly from the publication, then the number of patients reporting at least good pain relief or reporting improvement was used to calculate NNT. NNT was only calculated when the relative risk was statistically significant. NNH in this review indicates the number of patients that need to be treated for one patient to drop out due to adverse effects. The 95% confidence interval (CI) of NNT and NNH was calculated as the reciprocal value of the 95% CI for the absolute risk difference using the normal approximation. NNTs are expressed in the text as NNT (95% CI). Pooled raw data was used to obtain combined measures of NNTs assuming clinically homogeneous trials (Moore et al., 2002).

The outcome of a trial (positive or negative) was judged by the reviewers in those cases where authors' conclusions were at odds with the change in the primary outcome measure.

Heterogeneity was examined visually using L'Abbé plots (L'Abbé et al., 1987). An instrument suggested by Jadad et al. (1996) was used as a measure of quality. Validity tests (e.g. Smith et al., 2000) were not used.

3. Results

3.1. Study and patients characteristics of included trials

Eligible randomized placebo-controlled trials with references, study characteristics, and quality score are provided in Table 2. One hundred and five randomized, double-blind, placebo-controlled studies that met the inclusion and exclusion criteria were included. Fifty-nine used a cross-over and 46 a parallel design. Five studies used an active placebo. Twenty-six trials examined antidepressants (21 cross-over and five parallel design), 39 anticonvulsants (18 cross-over and 21 parallel design), 11 examined opioids, seven NMDA antagonists, nine mexiletine, four topical lidocaine, three cannabinoids, 11 capsaicin, and one a glycine antagonist. The trials included patients with central post-stroke pain, spinal cord injury pain, multiple sclerosis, painful polyneuropathy, post-herpetic neuralgia, phantom limb pain, post-mastectomy and post-surgical pain, brachial plexus avulsion, trigeminal neuralgia, HIV-neuropathy, and mixed neuropathic pain conditions. The trials are discussed below by drug class.

3.2. Antidepressants

Tricyclic antidepressants (TCAs) in controlled trials (Table 2) relieve central post-stroke pain, post-herpetic neuralgia, painful diabetic and non-diabetic polyneuropathy and post-mastectomy pain syndrome, but not spinal cord injury pain, phantom limb pain, or pain in HIV-neuropathy. The doses used in these negative trials may make these conclusions less compelling. Negative results in spinal cord injury pain could be related to low dosing (amitriptyline average 55 mg/day) (Cardenas et al., 2002), and those in phantom limb pain by a very low inclusion pain score criteria (2) which gives little room for pain reduction (Robinson et al., 2004). Across the different conditions which are relieved by TCAs the NNT ranges from 2 to 3.

In painful polyneuropathy, there is a trend towards better effect of balanced serotonin and noradrenaline reuptake inhibitors (NNT: 2.1 (1.8–2.6)) than of the mainly noradrenergic drugs (NNT: 2.5 (1.9–3.6)) (Sindrup et al., 2005). In post-herpetic neuralgia there is the same trend

(balanced TCA NNT: 2.5 (1.8–3.9) vs noradrenergic TCA NNT: 3.1 (2.2–5.5)).

The selective serotonin reuptake inhibitors (SSRIs) and the mixed serotonin noradrenaline reuptake inhibitors (SNRIs) have been adequately tested in painful polyneuropathy. For SSRIs, the overall NNT is nearly 7 and one of the three trials did not find better effect with active than placebo. The SNRI venlafaxine has an NNT in painful polyneuropathies of around 4. Bupropion, a noradrenaline and dopamine reuptake inhibitor, was reported-in a small trial of 41 patients—to relieve pain in a group of patients with neuropathic pain of different etiologies.

The NNH is 14.7 (10.2–25.2) for TCA, and for SNRI and SSRI the relative risk for trial withdrawal is not significant.

3.3. Anticonvulsants

The early trials on carbamazepine do not meet current methodological standards (e.g. use of validated outcome measures, sample size calculation, and adequate description of randomization procedure, statistical methods, and patient flow), but an attempt to calculate NNT gives a combined NNT in trigeminal neuralgia of 1.7 (1.3–2.2). In painful diabetic neuropathy, the NNT from one trial with 30 patients on 200–600 mg daily was 2.3 (1.6–3.9) and in post-stroke pain there was a small but not statistically significant effect of 800 mg daily with a NNT of 3.4 (1.7–105). The combined NNH for carbamazepine in neuropathic pain is 21.7 (12.6–78.5), based on a total of 152 patients. Randomized controlled trials comparing oxcarbazepine to carbamazepine have reported comparable analgesic effect between the two treatments with fewer side effects during oxcarbazepine (for review, see Beydoun and Kutluay (2002), Carrazana and Mikoshiba (2003)), but these trials have not yet been published fully.

Phenytoin had a positive effect on painful diabetic neuropathy in one trial (NNT: 2.1 (1.5–3.6)), while another showed no analgesic effect. In patients with acute flare-ups of various neuropathic pain conditions intravenous phenytoin 15 mg/kg over 2 h had a significant pain-relieving effect (McCleane, 1999a).

Valproate in three parallel group trials from the same centre with 43–57 patients had high efficacy in relieving pain in painful diabetic neuropathy and post-herpetic neuralgia in doses up to 1200 mg with very low NNTs, while a crossover trial of 31 patients from another centre found no difference between valproate 1500 mg and placebo in treating painful polyneuropathy and also showed no effect in the subgroup of patients with diabetic neuropathy. Valproate in doses up to 2400 mg/day was not significantly better than placebo in relieving pain in patients with spinal cord injuries.

Gabapentin has been studied in several large trials and has a documented moderate effect on pain and quality of life measures including mood and sleep disturbance in mixed neuropathic pain states, post-herpetic neuralgia, painful diabetic neuropathy, and spinal cord injury. The overall NNT for gabapentin in neuropathic pain, including all conditions, high as well as low doses, is 5.1 (4.1–6.8), but by excluding the study using only 900 mg/day, the study on mixed neuropathic pain, and including only the high dose of 2400 mg in Rice and Maton (2001), the combined NNT is 3.8 (3.1–5.1) The NNH for withdrawal for gabapentin is 26.1 (14.1–170). One small crossover study (19 completed patients) compared gabapentin (up to 1800 mg) with amitriptyline (up to 75 mg) in painful diabetic neuropathy (Morello et al., 1999). There was no significant difference in pain scores during gabapentin and amitriptyline treatment, pain intensity score change from baseline, and global ratings of pain relief (52% with at least moderate pain relief during gabapentin and 67% during amitriptyline) ($P > 0.1$). Both treatments caused similar rates of adverse events. Post hoc analysis revealed that a sample size of approximately 260 patients is necessary to provide 80% power to detect a mean difference of one third of the difference between mild and moderate pain at a 0.05 significance level.

The efficacy of gabapentin in combination with venlafaxine was studied in painful diabetic neuropathy (Simpson, 2001). In the second part of the study including 12 patients who did not respond to gabapentin, gabapentin plus venlafaxine improved pain and quality of life compared with gabapentin plus placebo. In another study, the combination of gabapentin and morphine was superior to gabapentin alone, morphine alone and the active placebo lorazepam in patients with post-herpetic neuralgia or painful diabetic neuropathy (Gilron et al., 2005).

Pregabalin in post-herpetic neuralgia and painful diabetic neuropathy has a combined NNT for doses ranging from 150 to 600 mg of 4.2 (3.4–5.4), comparable to the effect of gabapentin. The NNH for withdrawal was 11.7 (8.3–19.9) indicating a relatively high withdrawal rate (see Section 4).

Lamotrigine up to 400 mg daily has a pain relieving effect in trigeminal neuralgia as an add-on treatment (NNT: 2.1 (1.3–6.1)), in painful diabetic neuropathy (NNT: 4.0 (2.1–42)), and in central post-stroke pain. In HIV-associated painful sensory neuropathy, a small study showed a significant effect of lamotrigine 300 mg daily, but an extended larger study using 600 mg daily only demonstrated an effect on some secondary parameters in those patients receiving neurotoxic antiretroviral therapy. In spinal cord injury pain lamotrigine had no effect, although it had an effect on spontaneous pain in a subgroup of patients with incomplete injury and evoked pain.

Topiramate in doses up to 400 mg failed to relieve pain in three large trials including in total 1259 patients with painful diabetic neuropathy, while another trial found a significant effect (NNT: 7.4 (4.3–28.5)). The four topiramate studies had a high withdrawal rate due to side effects (NNH: 6.3 (5.1–8.1)).

3.4. Opioids

Intravenous opioid administration has been shown to have an effect on peripheral neuropathic pain (Rowbotham et al., 1991), on mixed neuropathic pain conditions (Dellemijn and Vanneste, 1997), and on some components of central pain (Attal et al., 2002). Oral long-term treatment with opioids, more relevant in chronic pain than intravenous administration, has only been tested using placebo-controlled designs in peripheral neuropathic pain conditions (Table 2).

Morphine was superior to placebo in patients with post-herpetic neuralgia, phantom limb pain, and painful diabetic neuropathy with an NNT of 2.5 (CI 1.9–3.4).

Oxycodone has been tested in post-herpetic neuralgia and painful diabetic neuropathy, with a NNT of 2.6 (CI 1.9–4.1), comparable to the effect of morphine.

Tramadol studied in two trials in painful polyneuropathy and in one trial in post-herpetic neuralgia had an overall NNT of 3.9 (CI 2.7–6.7). The study in post-herpetic neuralgia (Boureau et al., 2003) had a very high placebo responder rate.

The combined NNH was 9.0 (6.0–17.5) for tramadol, whereas the relative risk was non-significant for oxycodone and morphine.

3.5. NMDA antagonists

NMDA antagonists given as intravenous infusions may relieve neuropathic pains of different origin (Sang et al., 2000). Oral NMDA antagonists, dextromethorphan, riluzole and memantine have been studied mainly in small trials in neuropathic pain, with either no or minor pain relieving effect (Table 2). High dose dextromethorphan apparently has a clinically relevant effect in painful diabetic polyneuropathy (NNT: 2.5 (1.6–5.4)), but seems to lack efficacy in post-herpetic neuralgia. Memantine in doses 20–30 mg/day had no effect in post-herpetic neuralgia, painful diabetic neuropathy or phantom limb pain. Patients with different types of neuropathic pain achieved no pain relieving effect using riluzole 100 or 200 mg/day.

The NNH for dextromethorphan is 8.8 (5.6–21.1) and non-significant for memantine.

3.6. Miscellaneous

Mexiletine studies have inconsistent results. The overall relative risk in two studies in painful diabetic neuropathy is non-significant and in peripheral nerve injury the NNT is 2.2 (1.3–8.7)). Mexiletine seems to lack a pain relieving effect in HIV neuropathy, spinal cord injury, and neuropathic pain with prominent allodynia. Mexiletine has proarrhythmic properties and side effects may limit dose escalation, but it was generally well tolerated in these studies with only mild side effects (gastrointestinal and neurological complaints) and surprisingly high NNHs for withdrawal. A new sodium channel antagonist 4030W92 had no significant effect on neuropathic pain at 25 mg/day, but higher doses may be tolerable (Wallace et al., 2002a).

Topical lidocaine has been shown to reduce pain in patients with post-herpetic neuralgia and allodynia. Severity of allodynia seems not to be correlated with response to lidocaine patch. The patch has been shown to alleviate several pain qualities including non-allodynic pain components (Galer et al., 2002). An enriched enrolment study confirmed the pain relieving effect (Galer et al., 1999). The use of lidocaine patches was safe with no systemic adverse effects and high NNHs. In patients with various localized peripheral neuropathic pain syndromes including the presence of mechanical allodynia, lidocaine patch 5% as add-on therapy reduced ongoing pain and allodynia with a NNT of 4.4 (2.5–17.5). Ophthalmic anaesthesia with topical application of proparacaine, however, failed to relieve pain in trigeminal neuralgia (Kondziolka et al., 1994).

Cannabinoids have recently been studied in a few randomized trials. The tetrahydrocannabinol dronabinol 5–10 mg daily relieved pain in multiple sclerosis with a NNT of 3.4 (1.8–23.4) compared with placebo, and cannabinoids also relieved pain after brachial plexus avulsion and mixed neuropathic pain. Cannabinoids were generally well tolerated with gradually increasing doses.

Capsaicin applied topically relieved pain in post-herpetic neuralgia, nerve injury pain, and mixed neuropathic pain conditions and in diabetic neuropathy capsaicin relieved pain in three out of five studies, with a combined NNT of 6.7 (4.6–12) and NNH of 11.5 (8.1–19.8).

3.7. Quantitative data synthesis and homogeneity/heterogeneity

Combined NNTs and NNHs for different drug classes and neuropathic pain conditions are shown in Table 1 and Fig. 1. Heterogeneity was examined visually using L'Abbé plots (supplementary material). From dose response studies (Lesser et al., 2004; Oskarsson et al., 1997; Rice and Maton, 2001; Richter et al., 2005; Rowbotham et al., 2004; Sabatowski et al., 2004), it is evident that dose optimization and lack of such is a major cause of heterogeneity. In addition, L'Abbé plots suggest that both the drug classes used and the neuropathic pain diagnoses were other major reasons for heterogeneity, with studies in HIV neuropathy, central and mixed neuropathic pain conditions showing the lowest effect. The greatest variation was in NNT values within TCAs. Again differences in neuropathic pain diagnoses seemed to be responsible for part of this variability and optimal dosing by drug level measurements may be responsible for one outlier with a high percentage of responders. Excluding gabapentin non-responders in gabapentin/pregabalin studies and variability in quality score (Jadad et al., 1996) seemed not to be responsible for outliers. The placebo response varied greatly among trials (figure in supplementary material). Smaller cross-over trials tended to have lower NNT values (thus greater treatment effect) than

Table 1
Combined numbers needed to treat (with 95% confidence interval) to obtain one patient with more than 50% pain relief

	Neuropathic pain[a]	Central pain	Peripheral pain	Painful polyneuropathy	Post-herpetic neuralgia	Peripheral nerve injury	Trigeminal neuralgia	HIV neuropathy	Mixed neuropathic pain	NNH in neuropathic pain
Antidepressants										
TCA	3.1 (2.7–3.7)	4.0 (2.6–8.5)	2.3 (2.1–2.7)	2.1 (1.9–2.6)	2.8 (2.2–3.8)	2.5 (1.4–11)	ND	ns	NA	14.7 (10–25)
SSRI	6.8 (3.4–441)	ND	6.8 (3.4–441)	6.8 (3.4–441)	ND	ND	ND	ND	ND	ns
SNRI	5.5 (3.4–14)	ND	5.5 (3.4–14)	5.5 (3.4–14)	ND	NA	ND	ND	ND	ns
DNRI	1.6 (1.3–2.1)	ND	ND	ND	ND	ND	ND	ND	1.6 (1.3-2.1)	ns
Antidepressants	3.3 (2.9–3.8)	4.0 (2.6–8.5)	3.1 (2.7–3.7)	3.3 (2.7–4.1)	2.8 (2.2–3.8)	2.5 (1.4–11)	ND	ns	1.6 (1.3–2.1)	16.0 (12–25)
Anticonvulsants										
Carbamazepine	2.0 (1.6–2.5)	3.4 (1.7–105)	2.3 (1.6–3.9)	2.3 (1.6–3.9)	ND	ND	1.7 (1.3–2.2)	ND	NA	21.7 (13–79)
Phenytoin	2.1 (1.5–3.6)	ND	2.1 (1.5–3.6)	2.1 (1.5–3.6)	ND	ND	ND	ND	ND	ns
Lamotrigine	4.9 (3.5–8.1)	ns	4.0 (2.1–42)	4.0 (2.1–42)	ND	ND	2.1 (1.3–6.1)	5.4 (3.1–20)	ns	ns
Valproate	2.8 (2.1–4.2)	ns	2.4 (1.8–3.4)	2.5 (1.8–4.1)	2.1 (1.4–4.2)	ND	ND	ND	ND	ns
Gabapentin, pregabalin	4.7 (4.0–5.6)	NA	4.3 (3.7–5.2)	3.9 (3.2–5.1)	4.6 (3.7–6.0)	NA	ND	ND	8.0 (4.8–24)	17.8 (12–30)
Topiramate	7.4 (4.3–28)	ND	7.4 (4.3–28)	7.4 (4.3–28)	ND	ND	NA	ND	ND	6.3 (5–8)
Anticonvulsants	4.2 (3.8–4.8)	ns	4.1 (3.6–4.8)	3.9 (3.3–4.7)	4.4 (3.6–5.6)	NA	1.7 (1.4–2.2)	5.4 (3.1–20)	10.0 (5.9–32)	10.6 (9–13)
Opioids										
Opioids	2.5 (2.0–3.2)	ND	2.7 (2.1–3.6)	2.6 (1.7–6.0)	2.6 (2.0–3.8)	3.0 (1.5–74)	ND	ND	2.1 (1.5–3.3)	17.1 (10–66)
Tramadol	3.9 (2.7–6.7)	ND	3.9 (2.7–6.7)	3.5 (2.4–6.4)	4.8 (2.6–27)	ND	ND	ND	ND	9.0 (6–18)
NMDA antagonists										
Dextromethorphan	4.4 (2.7–12)	ND	3.4 (2.2–7.6)	2.5 (1.6–5.4)	ns	ND	ND	ND	ns	8.8 (6–21)
Memantine	ns	ND	ns	ns	ns	ns	ND	ND	ND	ns
NMDA antagonists	7.6 (4.4–27)	ND	5.5 (3.4–14)	2.9 (1.8–6.6)	ns	ns	ND	ND	ns	12.5 (8–36)
Various										
Mexiletine	7.8 (4.0–129)	NA	5.2 (2.9–26)	ns	ND	2.2 (1.3–8.7)	ND	ns	NA	ns
Topical lidocaine	4.4 (2.5–17)	ND	NA	ND	NA	ND	ND	NA	4.4 (2.5–17)	ns
Cannabinoids	ns	3.4 (1.8–23)	ND	ND	ND	ND	ND	ND	9.5 (4.1–∞)	ns
Topical capsaicin	6.7 (4.6–12)	ND	6.7 (4.6–12)	11 (5.5–317)	3.2 (2.2–5.9)	6.5 (3.4–69)	ND	NA	NA	11.5 (8–70)

NNH, combined numbers needed to harm (95% confidence interval) to obtain one patients to withdraw because of side effects. TCA, tricyclic antidepressants; SNRI, serotonin noradrenaline reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors; DNRI, dopamine noradrenaline reuptake inhibitors; ND, no studies done; NA, dichotomized data are not available; ns, relative risk not significant.

[a] Heterogeneity across different pain conditions.

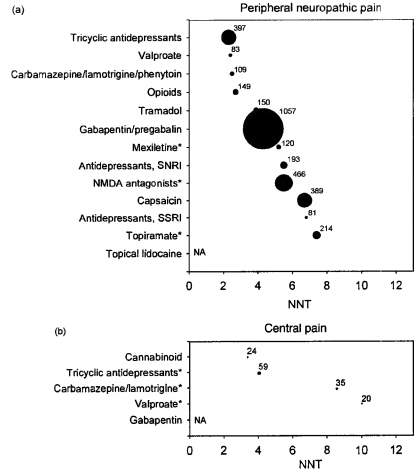

Fig. 1. Numbers needed to treat in peripheral and central neuropathic pain. Combined numbers needed to treat (NNT) to obtain one patient with more than 50% pain in (a) peripheral neuropathic pain (painful polyneuropathy, postherpetic neuralgia, and peripheral nerve injury pain) and (b) central pain (central post-stroke pain, pain following spinal cord injury and multiple sclerosis). SNRI, serotonin noradrenaline reuptake inhibitors; SSRI, selective serotonin reuptake inhibitor. Circle size and related numbers indicate number of patients who have received active treatment. *At least half of conducted trials showed no significant effect.

larger parallel group trials. The differences in NNT values based on the intention-to-treat population as opposed to the completed population can be estimated by calculating NNTs in studies with a parallel group design and comparing it with the NNT using the completed population. This is, however, not possible based on the reports, as most studies carry forward the pain ratings for patients who do not complete the study, and use these data in the analysis. But based on the 'worst case', i.e. assuming that all patients withdrawn are non-responders, the NNT for pregabalin based on the completed population is 3.4 (2.7–4.3) compared with 4.2 (3.4–5.4) based on the intention-to-treat population.

4. Discussion

4.1. Numbers needed to treat and harm

This meta-analysis using numbers needed to treat (NNT) shows that it is possible to distinguish pharmacological treatment efficacy for different drugs as evidenced by NNT values which varied from 1.2 to non-significant relative risks. The question is whether the NNT method permits generation of a treatment algorithm for neuropathic pain.

The NNT method for comparing drugs can be criticized for various reasons:

1. The relative efficacy and safety is derived from placebo comparisons of each active drug. Trials which do not compare with placebo are therefore excluded.
2. Calculation of NNT is done retrospectively from studies with different cut-off points for defining pain relief.
3. Pain relief per se may be a crude measure, which does not take other specific measures into account like impact on daily living and quality of life.
4. Use of different inclusion and exclusion criteria makes it difficult to compare and to combine studies.
5. NNT values cannot be calculated when conversion to dichotomous data is not possible.

6. As for all meta-analyses there is a risk that NNT values will overestimate the efficacy if negative trials are not published.

The advantage of using NNTs is that they provide a clinically meaningful measure of effect and risk of each drug, and data from different trials, even with different outcome measures, can be pooled. The legitimacy of the pooling depends on similar therapeutic context, patients, duration of study, and clinical homogeneity.

It is important to bear in mind that some of these NNT values in neuropathic pain are obtained from studies of variable quality and most available studies are short-term studies with no information on long-term effect.

The choice of a 33 or 50% cutoff when calculating NNTs has little impact on NNT values because efficacy of both active and placebo treatments changes (McQuay and Moore, 1998).

In the present analysis, calculation of NNH was based on patients that withdrew from the study because of adverse effects, and we have not included other side-effects that may be bothersome for long-term treatment, e.g. constipation and dizziness. The design itself may influence the NNH value. A compound with a high NNH value from a short lasting trial may still be unsuitable for long-term use. An example is chronic phenytoin treatment causing gingival hyperplasia, hirsutism, polyneuropathy and hepatotoxicity (Rogvi-Hansen and Gram, 1995). Compounds may also cause serious side effects not reflected in the NNH value, e.g. sudden death associated with TCA (Ray et al., 2004) or Stevens-Johnson syndrome after treatment with lamotrigine (Mackay et al., 1997).

4.2. Quality of randomized controlled trials

Quality of trials varies for obvious reasons and the variation in quality may lead to bias in meta-analyses (Alderson et al., 2003; Detsky et al., 1992; Moher et al., 1999) and existing criteria have their limitations. It is possible that we had obtained other results if more stringent quality and validity criteria were used (Detsky et al., 1992; Smith et al., 2000).

4.3. Heterogeneity and selection bias

The major cause of heterogeneity was dose, pain diagnosis, and study design, with small, cross-over trials having the lowest NNT values. There was also a large variation in placebo response among studies.

Some of the studies on gabapentin and pregabalin excluded patients who failed to respond to previous treatment with gabapentin, which may bias efficacy comparisons with other drugs using NNT values. Calculating the impact of this enriched enrolment on the overall NNT, taking the worst case scenarios, the NNT for pregabalin is 5.4 (4.3–7.1) compared to 4.2 (3.4–5.4). However, a recent trial showed an NNT of 4.2 (2.7–9.4) without excluding gabapentin non-responders (Richter et al., 2005).

Combining cross-over and parallel designed studies in meta-analyses is another concern (Elbourne et al., 2002), and the generally lower NNT value with the tricyclic antidepressants may in part be due to the fact that 19/23 trials were cross-over trials compared to 2/12 of the gabapentin/pregabalin trials.

Selection bias may be present and includes publication bias, which arises from higher tendency for studies with a statistically significant effect of treatment to be published thereby introducing bias in meta-analyses (Moher et al., 1999). We have no direct evidence that this problem applies to this data set, and indeed there are a number of negative studies included in the analysis.

4.4. Treatment algorithm

Based on the available randomized clinical trials, it is of interest to see if an evidence-based approach for managing neuropathic pain is possible. In choice of treatment for neuropathic pain a set of different criteria are relevant including:

1. Consistent outcome in high-quality randomized controlled trials.
2. High degree of pain relief and superiority to existing treatments.
3. Persistent pain relieving effect.
4. Few and only mild side effects.
5. Effect on quality of life.
6. Low cost.

Because of heterogeneity across treatment of different pain conditions, algorithms need to be tailored to specific diseases or disease categories.

There are no existing data which permit generation of an algorithm based on a combination of all the above criteria mainly because of a lack of comparative studies between existing and new compounds using the same set of primary and secondary endpoints.

A treatment algorithm for peripheral neuropathic pain (painful neuropathy, painful diabetic neuropathy, postherpetic neuralgia and peripheral nerve injury pain) is described below. The algorithm deals only with pharmacological considerations. Needless to say for all pain conditions, non-pharmacological treatments should be considered. The algorithm can be described in a hierarchical fashion in which increasing numbers of criteria are taking into account:

If only one set of criteria: pain relief is used then the list of drugs for neuropathic pain look like this: TCA > opioids ≥ tramadol ≥ gabapentin/pregabalin.

If the criteria for efficacy are based on both pain relief and quality of life measures then such data are not existent

for several of the old compounds such as TCA, carbamazepine, and phenytoin and the list is likely to look as follows: gabapentin/pregabalin > tramadol > opioids > TCA.

If additional requirements such as side effects and study design are taken into account then important and occasionally dangerous side effects of TCA and strong opioids need to be considered. Under these conditions the algorithm for peripheral neuropathic pain may be as shown in Fig. 2. The effect of gabapentin and TCAs are documented in large and numerous trials with good quality and with consistent outcomes. One small trial compared gabapentin and amitriptyline and found no difference in pain scores (Morello et al., 1999). TCAs have lower NNT values than gabapentin/pregabalin but as discussed above part of this difference may be due to differences in study design. Furthermore, as gabapentin/pregabalin have higher NNH values and lack serious adverse effects it thus seems reasonable to have these two drug classes as first line treatment of peripheral neuropathic pain. As new studies on SNRIs (with fewer side effects than TCAs) are emerging, these drugs may replace TCAs. Tramadol and oxycodone may be considered second or third line drugs. The NNT values are for these and other opioids low, and a direct comparison study show equal or slightly better effect of morphine compared to gabapentin (Gilron et al., 2005). Anxieties about dependence, cognitive impairment, and tolerance issues, although there is no hard evidence for such problems, may make opioids a less attractive choice. Combination of drugs targeting separate mechanisms theoretically may improve treatment, but, except for the combination of gabapentin with venlafaxine or morphine, evidence for this is still lacking.

In trigeminal neuralgia, carbamazepine is suggested as first choice because of consistent outcome with a low NNT, although in studies of varying quality. Oxcarbazepine (as yet no published trials) may be an alternative.

In central pain few studies exist and it is unknown whether an effective treatment in one central pain condition can be expected to be effective in other central pain conditions. Therefore, a treatment algorithm in these pain conditions needs to be based partly on the experience in peripheral neuropathic pain conditions, until further studies arise. TCAs are often not tolerated in the elderly patients with stroke, so, in these cases, gabapentin/pregabalin seems to be first choice. TCAs, lamotrigine, cannabinoids, tramadol, and opioids may be second choice.

For future trials, we encourage authors to:

(1) report the trial to a central database (DeAngelis et al., 2004);
(2) to follow Good Clinical Practice (GCP) requirements (ICH, 1997; Jorgensen et al., 2004);
(3) to follow the guidelines in the consort statement (Moher et al., 2001);
(4) to do more head-to head comparisons.

The relative efficacy rank order obtained by the NNT method agree to some extent with the few head-to-head comparisons performed in neuropathic pain (Gilron et al., 2005; Morello et al., 1999; Raja et al., 2002; Sindrup et al., 2003), but to look for subtle differences head-to-head comparisons are needed. Furthermore, it may be inappropriate to use of placebo in severe pain, for instance in trigeminal neuralgia, making it difficult to obtain relative efficacy estimates based on placebo comparisons. This

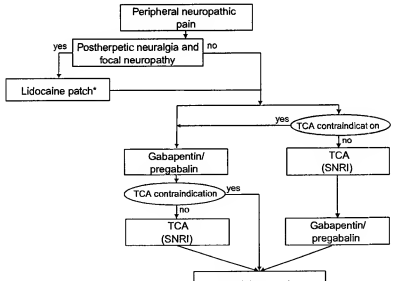

Fig. 2. Treatment algorithm. Proposed algorithm for the treatment of peripheral neuropathic pain. TCA, tricyclic antidepressants; SNRI, serotonin noradrenaline reuptake inhibitors. *Pain relieving effect of topical lidocaine has been shown in patients with allodynia.

Table 2
Randomized, double-blind, placebo-controlled trials of different drugs in various neuropathic pain conditions

Active drug daily drug dose	Study quality rating nos	Design patient	Outcome	Pain relief		NNT (95% CI)	Drop outs side effects		NNH (95% CI)
				Active	Placebo		Active	Placebo	
Antidepressants									
Central post-stroke pain									
Amitriptyline, 75 mg	Leijon and Boivie, 1989, 4	Cross-over, 15	Ami > pla	10/15	1/14	1.7 (1.2–3.1)	0/15	0/15	ns
Spinal cord injury pain									
Amitriptyline, average 50 mg	Cardenas et al., 2002, 4	Parallel, 84	Ami = pla	8/44	2/40	ns	7/44	2/40	ns
Painful polyneuropathy									
Imipramine, 100 mg	Kvinesdal et al., 1984, 4	Cross-over, 12	Imi > pla	7/12	0/12	1.7 (1.2–3.3)	1/13	0/13	ns
Nortriptyline, 30 mg	Gomez-Perez et al., 1985, 4	Cross-over, 18	Nor > pla	16/18	1/18	1.2 (1.0–1.5)	0/18	0/18	ns
Amitriptyline, average 90 mg	Max et al., 1987, 4	Cross-over, 29	Ami > pla	15/29	1/29	2.1 (1.5–3.5)	3/32	2/31	ns
Imipramine, average 200 mg	[a]Sindrup et al., 1990a, 4	Cross-over, 20	Imi > pla	17/19	3/20	1.3 (1.0–1.9)	7/29	0/20	4.1 (2.5–11.7)
Clomipramine, 75 mg	[a]Sindrup et al., 1990b, 4	Cross-over, 19	Clo > pla	10/19	1/19	2.1 (1.4–4.4)	3/24	0/20	ns
Desipramine, 200 mg	[a]Sindrup et al., 1990b, 4	Cross-over, 19	Des > pla	7/19	1/19	3.2 (1.8–13.0)	3/23	0/20	ns
Desipramine, average 201 mg	Max et al., 1991, 3	Cross-over, 20	Des > pla	11/20	2/20	2.2 (1.4–5.1)	2/24	1/24	ns
Imipramine, 150 mg	[a]Sindrup et al., 1992a, 4	Cross-over, 18	Imi > pla	8/18	2/18	3.0 (1.7–16.2)	1/22	0/20	ns
Amitriptyline, 75 mg	Vrethem et al., 1997, 4	Cross-over, 33	Ami > pla	22/33	8/33	2.4 (1.6–4.8)	3/36	0/33	ns
Maprotiline, 75 mg	Vrethem et al., 1997, 4	Cross-over, 33	Map > pla	14/33	8/33	ns	1/34	0/33	ns
Imipramine, 150 mg	Sindrup et al., 2003, 5	Cross-over, 29	Imi > pla	14/29	2/29	2.4 (1.6–4.8)	0/37	2/40	ns
Paroxetine, 40 mg	[a]Sindrup et al., 1990a, 4	Cross-over, 20	Par > pla	10/20	3/20	2.9 (1.6–12.4)	0/20	0/20	ns
Fluoxetine, 40 mg	Max et al., 1992, 3	Cross-over, 46	Flu = pla	22/46	19/46	ns	3/54	2/54	ns
Citalopram, 40 mg	Sindrup et al., 1992b, 4	Cross-over, 15	Cit > pla	3/15	1/15	ns	2/18	0/18	ns
Venlafaxine, 225 mg	Sindrup et al., 2003, 5	Cross-over, 30	Ven > pla	8/30	2/29	5.1 (2.6–68.8)	4/40	2/40	ns
Venlafaxine, 75–225 mg	Rowbotham et al., 2004, 4	Parallel, 244	Ven > pla	78/163	27/81	6.9 (3.7–58.6)	14/163	3/81	ns
St. John's Wort	Sindrup et al., 2000, 5	Cross-over, 47	SJW = pla	9/47	2/47	6.7 (3.6–44.4)	1/50	1/52	ns
Postherpetic neuralgia									
Amitriptyline, average 73 mg	Watson et al., 1982, 4	Cross-over, 24	Ami > pla	16/24	1/24	1.6 (1.2–2.4)	1/24	0/24	ns
Amitriptyline, average 65 mg	Max et al., 1988, 3	Cross-over, 34	Ami > pla	15/34	5/25	4.1 (2.1–82.1)	5/35	3/30	ns
Desipramine, average 167 mg	Kishore-Kumar et al., 1990, 3	Cross-over, 19	Desi > pla	12/19	2/19	1.9 (1.3–3.7)	5/23	3/21	ns
Nortriptyline, average 89 mg	[a]Raja et al., 2002, 5	Cross-over, 56	TCA > Pla	18/56	4/57	4.0 (2.6–8.9)	7/59	1/57	9.9 (5.3–84.6)
Desipramine, average 63 mg									
Phantom limb pain									
Amitriptyline, 10–125 mg	Robinson et al., 2004, 4	Parallel, 39	Ami = pla	NA	NA	NA	2/20	0/19	ns
Postmastectomy pain									
Amitriptyline, 100 mg	[a]Kalso et al., 1995, 3	Cross-over, 15	Ami > pla	8/15	2/15	2.5 (1.4–10.6)	4/20	0/20	5 (2.7–40.5)
Venlafaxine, 37.5–75 mg	Tasmuth et al., 2002, 4	Cross-over, 13	Ven = pla	11/13	NA	NA	1/15	0/13	ns
HIV-neuropathy									
Amitriptyline, 25–100 mg	Kieburtz et al., 1998, 5	Parallel, 98	Ami = pla	23/46	24/50	ns	3/46	1/50	ns
Amitriptyline, 25–75 mg *Mixed patients*	Shlay et al., 1998, 4	Parallel, 110	Ami = pla	27/58	24/50	ns	NA	NA	NA
Clomipramine, 25–100 mg	Panerai et al., 1990, 3	Cross-over, 24	Clo > pla	NA	NA	NA	0/27	1/27	ns
Nortriptyline, 25–100 mg	Panerai et al., 1990, 3	Cross-over, 24	Nor > Pla	NA	NA	NA	2/27	1/27	ns
Bupropion, 300 mg	[b]Semenchuk et al., 2001, 3	Cross-over, 41	Bup > pla	30/41	4/41	1.6 (1.3–2.1)	2/41	1/40	ns

(*continued on next page*)

Table 2 (*continued*)

Active drug daily drug dose	Study quality rating	Design patient nos	Outcome	Pain relief		NNT (95% CI)	Drop outs side effects		NNH (95% CI)
				Active	Placebo		Active	Placebo	
Anticonvulsants									
Central post-stroke pain									
Carbamazepine, 800 mg	Leijon and Boivie, 1989, 4	Cross-over, 15	Carb=pla	5/14	1/15	3.4 (1.7–105)	1/15	0/15	ns
Lamotrigine, 200 mg	Vestergaard et al., 2001, 5	Crossover, 30	Ltg>pla	NA	NA	NA	3/30	0/27	ns
Spinal cord injury pain									
Lamotrigine, 200–400 mg	[f]Finnerup et al., 2002, 5	Crossover, 22	Ltg=pla	4/21	4/21	ns	1/27	2/28	ns
Valproate, 600–2400 mg	Drewes et al., 1994, 3	Crossover, 20	Val=pla	6/20	4/20	ns	0/20	0/20	ns
Gabapentin, up to 3600 mg	Levendoglu et al., 2004, 4	Crossover, 20	Gab>pla	NA	NA	NA	0/20	0/20	ns
Painful polyneuropathy									
Carbamazepine, 200–600 mg	[cd]Rull et al., 1969, 2	Crossover, 30	Carb>pla	26/42	8/45	2.3 (1.6–3.9)	2/30	0/30	ns
Carbamazepine, 600 mg	[c]Wilton, 1974, 3	Crossover, 40	Carb>pla	NA	NA	NA	NA	NA	NA
Phenytoin, 300 mg	[c]Saudek et al.1977, 2	Crossover, 12	Phe=pla	NA	NA	NA	2/12	0/12	ns
Phenytoin, 300 mg	[c]Chadda and Mathur, 1978, 2	Crossover, 38	Phe>pla	28/38	10/38	2.1 (1.5–3.6)	0/38	0/38	ns
Lamotrigine, 50–400 mg	Eisenberg et al., 2001, 5	Parallel, 59	Lam>pla	12/29	5/30	4.0 (2.1–42)	2/29	2/30	ns
Valproate, 1200 mg	Kochar et al., 2002, 4	Parallel, 57	Val>pla	24/29	5/28	1.5 (1.2–2–2)	1/29	0/28	ns
Valproate, 1500 mg	Otto et al., 2004, 5	Crossover, 31	Val=pla	8/31	3/31	ns	2/36	1/37	ns
Valproate, 500–1000 mg	[a]Kochar et al., 2004, 4	Parallel, 43	Val>pla	NA/22	NA/21	2 (1–3)	1/22	0/21	ns
Gabapentin, up to 3600 mg	Backonja et al., 1998, 5	Parallel, 165	Gab>pla	47/84	25/81	4.0 (2.5–9.6)	7/84	5/81	ns
Gabapentin, 900 mg	[c]Gorson et al., 1999, 2	Crossover, 40	Gab=pla	17/40	9/40	ns	0/40	0/40	ns
Gabapentin, 3600 mg	Simpson, 2001, 2	Parallel, 60	Gab>pla	15/30	7/30	3.8 (2.0–30.9)	2/30	2/30	ns
Pregabalin, 300 mg	[b]Rosenstock et al., 2004, 4	Parallel, 146	Pre>pla	30/76	10/70	4.0 (2.6–8.7)	8/76	2/70	ns
Pregabalin, (150) 300, 600 mg	[b]Lesser et al., 2004, 5	Parallel, 337	Pre>pla	76/163	17/97	3.4 (2.5–5.5)	13/163	3/97	ns
Pregabalin, (150) 600 mg	Richter et al., 2005, 5	Parallel, 246	Pre>pla	32/82	13/85	4.2 (2.7–9.4)	7/82	4/84	ns
Topiramate 400 mg	Raskin et al., 2004	Parallel, 323	Top>pla	74/214	23/109	7.4 (4.3–28.5)	52/214	9/109	6.2 (4.2–12.0)
Topiramate 100, 200, 400 mg	Thienel et al., 2004	Parallel, 1259	Top=pla	NA	NA	NA	213/878	32/381	6.3 (5.0–8.4)
Postherpetic neuralgia									
Gabapentin, 1200–3600 mg	Rowbotham et al., 1998, 5	Parallel, 229	Gab>pla	47/113	14/116	3.4 (2.5–5.4)	21/113	14/116	ns
Gabapentin, 1800–2400 mg	[f]Rice and Maton, 2001, 5	Parallel, 334	Gab>pla	74/223	15/111	5.1 (3.5–9.3)	34/223	7/111	11.2 (6.5–41.6)
Pregabalin, 300–600 mg	[f]Dworkin et al., 2003, 4	Parallel, 173	Preg>pla	44/89	17/84	3.4 (2.3–6.4)	28/89	4/84	3.7 (2.7–6.2)
Pregabalin, 150, 300 mg	[f]Sabatowski et al., 2004, 5	Parallel, 238	Preg>Pla	42/157	8/81	5.9 (3.8–13.6)	21/157	8/81	ns
Valproate, 1000 mg	Kochar et al., 2005, 3	Parallel, 45	Val>pla	13/23	2/22	2.1 (1.4–4.2)	1/22	0/22	ns
Phantom limb pain									
Gabapentin, 1800 – 2400 mg	Bone et al., 2002, 5	Crossover, 19	Gab>pla	NA	NA	NA	0/19	0/19	ns
Trigeminal neuralgia									
Carbamazepine, up to 800 mg	[c]Campbell et al., 1966, 4	Crossover, 70	Carb>pla	NA	NA	NA	1/77	0/77	ns
Carbamazepine, 600 mg	[c]Rockliff and Davis, 1966, 3	Crossover, 9	Carb>pla	NA	NA	NA	NA	NA	NA
Carbamazepine, 400–1000 mg	[ce]Killian and From, 1968, 4	Crossover, 27	Carb>pla	19/27	0/27	1.4 (1.1–1.9)	3/30	0/30	ns
Carbamazepine, 100–2400 mg	[ch]Nicol, 1969, 2	Crossover, 44	Carb>pla	27/37	6/24	2.1 (1.4–3.9)	NA	NA	NA
Lamotrigine, up to 400 mg	[z]Zakrzewska et al., 1997, 4	Crossover, 14	Lam>pla	7/13	1/14	2.1 (1.3–6.1)	0/14	0/14	ns
HIV-neuropathy									
Lamotrigine, 300 mg	Simpson et al., 2000, 5	Parallel, 42	Lam>pla	NA	NA	NA	6/20	0/22	3.3 (2.0–10.1)
Lamotrigine, up to 600 mg	Simpson et al., 2003, 3	Parallel, 227	Lam=pla	86/150	30/77	5.4 (3.1–20.4)	10/150	7/77	ns
Gabapentin, 1200–2400 mg	Hahn et al., 2004, 5	Parallel, 26	Gab=pla	NA	NA	NA	1/15	0/11	ns
Mixed patients									
Carbamazepine, 400–600 mg	[n]Harke et al., 2001, 2	Parallel, 43	Carb>pla	NA	NA	NA	NA	NA	NA

Lamotrigine, 200 mg	[k]McCleane, 1999b, 5	Parallel, 100	Lam=pla	0/50	0/50	ns	5/50	5/50	ns
Gabapentin, 900–2400 mg	[b]Serpell, 2002, 5	Parallel, 307	Gab>pla	32/153	21/152	ns	24/153	25/152	ns
Gabapentin, 3200 mg	Gilron et al., 2005, 5	Cross-over, 41	Gab=pla	27/44	13/42	3.3 (2.0–9.7)	4/48	1/44	ns
Opioids									
Painful polyneuropathy									
Tramadol, 200–400 mg	[a]Harati et al., 1998, 5	Parallel, 127	Tra>pla	43/63	23/64	3.1 (2.1–6.3)	9/63	1/64	7.9 (4.6–28.1)
Tramadol, 200–400 mg	Sindrup et al., 1999, 5	Cross-over, 34	Tra>pla	11/34	3/33	4.3 (2.4–21.1)	7/43	2/40	ns
CR Oxycodone, 20–80 mg	[a]Watson et al., 2003, 5	Cross-over, 36	Oxy>pla	21/34	8/34	2.6 (1.7–6.0)	7/45	4/45	ns
CR Oxycodone, average 37 mg	Gimbel et al., 2003, 5	Parallel, 159	Oxy>pla	NA	NA	NA	7/82	4/77	ns
Postherpetic neuralgia									
Oxycodone, 20–60 mg	Watson and Babul, 1998, 4	Cross-over, 38	Oxy>pla	22/38	7/38	2.5 (1.7–5.1)	5/50	3/50	ns
Morphine, average 91 mg	[a]Raja et al., 2002, 5	Cross-over, 65	Opio>pla	29/65	4/57	2.7 (1.9–4.2)	7/66	1/57	11.3 (5.9–147)
Methadone, average 15 mg									
Tramadol 300–400 mg	Bnureau et al., 2003, 5	Parallel, 127	Tra>pla	41/53	31/55	4.8 (2.6–26.9)	6/64	0/63	10.7 (6.1–44.8)
Phantom limb pain									
Retarded morphine, 70–300 mg	Huse et al., 2001, 4	Cross-over, 12	Mor>pla	5/12	1/12	3.0 (1.5–73.8)	NA	NA	NA
Mixed patients									
Sust. Release morphine 60–90 mg	[b]Harke et al., 2001, 2	Parallel, 38	Mor=pla	NA	NA	NA	NA	NA	NA
Methadone 10/20 mg	[bm]Morley et al., 2003, 5	Cross-over, 18	Met>pla	NA	NA	NA	NA	NA	NA
Morphine, 120 mg	Gilron et al., 2005, 5	Cross-over, 41	Mor>pla	35/44	13/42	2.1 (1.5–3.3)	5/49	1/44	ns
NMDA antagonists									
Painful polyneuropathy									
Dextromethorphan, average 381 mg	Nelson et al., 1997, 5	Cross-over, 13	Dex>pla	7/13	0/13	1.9 (1.2–3.7)	0/13	0/13	ns
Dextromethorphan, 400 mg	Sang et al., 2002, 4	Cross-over, 19	Dex>pla	13/19	7/19	3.2 (1.6–68.6)	0/19	0/19	ns
Memantine, 55 mg	Sang et al., 2002, 4	Cross-over, 19	Mem=pla	9/19	7/19	ns	1/23	0/19	ns
Postherpetic neuralgia									
Dextromethorphan, average 439 mg	Nelson et al., 1997, 5	Cross-over, 13	Dex=pla	5/13	3/13	ns	4/18	0/15	4.5 (2.4–33.2)
Dextromethorphan, 400 mg	Sang et al., 2002, 4	Cross-over, 17	Dex=pla	5/17	2/17	ns	1/21	0/17	ns
Memantine, 20 mg	Eisenberg et al., 1998, 4	Parallel, 24	Mem=pla	2/12	2/12	ns	3/12	1/12	ns
Memantine, 35 mg	Sang et al., 2002, 4	Cross-over, 17	Mem=pla	2/17	2/17	ns	0/17	0/17	ns
Phantom limb pain									
Memantine, 20 mg	Nikolajsen et al., 2000, 4	Cross-over, 15	Mem=pla	1/15	1/15	ns	2/15	2/15	ns
Memantine, 30 mg	Maier et al., 2003, 5	Parallel, 18	Mem=pla	10/18	6/18	ns	2/18	0/18	ns
Mixed patients									
Riluzole, 100 mg	Galer et al., 2000, 3	Cross-over, 22	Ril=pla	0/22	2/22	ns	NA	NA	NA
Riluzole, 200 mg	Galer et al., 2000, 3	Cross-over, 21	Ril=pla	NA	NA	NA	NA	NA	NA
Dextromethorphan, 81 mg	McQuay et al., 1994, 4	Cross-over, 17	Dex=pla	6/17	6/17	ns	5/17	0/17	3.4 (2–12.9)
Mexiletine									
Spinal cord injury pain									
Mexiletine, 450 mg	Chiou-Tan et al., 1996, 3	Cross-over, 11	Mex=pla	NA	NA	NA	0/14	0/14	ns
Painful polyneuropathy									
Mexiletine, 10 mg/kg	Dejgard et al., 1988. 3	Cross-over, 16	Mex>pla	NA	NA	NA	0/19	0/19	ns
Mexiletine, 225,450,675 mg	Stracke et al., 1992, 3	Parallel, 95	Mex=pla	NA	NA	NA	NA	NA	NA
Mexiletine, 225,450,675 mg	[n]Oskarsson et al., 1997, 4	Parallel, 126	Mex=pla	65/95	21/31	ns	8/95	1/31	ns
Mexiletine, 600 mg	Wright et al., 1997, 5	Parallel, 31	Mex=pla	7/14	4/15	ns	2/15	3/16	ns

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Table 2 (*continued*)

Active drug daily drug dose	Study quality rating	Design patient nos	Outcome	Pain relief		NNT (95% CI)	Drop outs side effects		NNH (95% CI)
				Active	Placebo		Active	Placebo	
Peripheral nerve injury									
Mexiletine, 750 mg	Chabal et al., 1992, 3	Cross-over, 11	Mex > pla	6/11	1/11	2.2 (1.3–8.7)	0/11	0/11	ns
HIV-neuropathy									
Mexiletine, up to 600mg	Kieburtz et al., 1998, 5	Parallel, 98	Mex = pla	22/48	24/50	ns	4/48	1/50	ns
Mexiletine, up to 600 mg	Kemper et al., 1998, 3	Cross-over, 16	Mex = pla	NA	NA	NA	2/22	9/22	ns
Mixed patients									
Mexiletine, 900 mg	[bm]Wallace et al., 2000, 3	Cross-over, 20	Mex = pla	NA	NA	NA	0/20	0/20	ns
Topical lidocaine									
Postherpetic neuralgia									
Lidocaine gel, 5%	[b]Rowbotham et al., 1995, 4	Cross-over, 39	Lid > pla	NA	NA	NA	1/46	2/46	ns
Lidocaine patch, 5%	[b]Rowbotham et al., 1996, 4	Cross-over, 35	Lid > pla	NA	NA	NA	0/35	0/35	ns
HIV-neuropathy									
Lidocaine gel, 5%	Estanislao et al., 2004, 3	Cross-over, 56	Lid = pla	NA	NA	NA	2/61	0/59	ns
Mixed patients									
Lidocaine patch, 5%	[aop]Meier et al., 2003, 5	Cross-over, 40	Lid > pla	12/39	3/37	4.4 (2.5–17.5)	0/51	1/58	ns
Cannabinoids									
Multiple sclerosis									
Dronabinol 5–10 mg	Svendsen et al., 2004, 5	Cross-over, 24	Can > pla	11/24	4/24	3.4 (1.8–23.4)	0/24	0/24	ns
Brachial plexus avulsion									
THC 129,6 mg +/-CBD 120 mg	Berman et al., 2004, 4	Parallel, 141	Can > pla	1/93	0/48	ns	1/93	1/48	ns
Mixed patients									
CT3 80 mg	[ap]Karst et al., 2003, 5	Cross-over, 21	Can > pla	2/19	0/19	ns	1/20	2/20	ns
Capsaicin									
Painful polyneuropathy									
Capsaicin, 0.075% qid	Chad et al., 1990, 2	Parallel, 46	Caps = pla	17/28	11/26	ns	NA	NA	NA
Capsaicin, 0.075% qid	Scheffler et al., 1991, 3	Parallel, 54	Caps > pla	17/19	11/22	2.5 (1.6–6.9)	2/28	0/26	ns
Capsaicin, 0.075% qid	Capsaicin Study Group, 1991, 4	Parallel, 277	Caps > pla	65/138	57/139	ns	18/138	5/139	10.6 (6.3–33.0)
Capsaicin, 0.075% qid	Tandan et al., 1992, 3	Parallel, 22	Caps > pla	6/11	2/11	ns	1/11	0/11	ns
Capsaicin, 0.075% qid	[a]Low et al., 1995, 3	Parallel, 40	Caps = pla	23/40	26/40	ns	NA	NA	NA
Postherpetic neuralgia									
Capsaicin, 0.075% tid/qid	Bernstein et al., 1989, 4	Parallel, 32	Caps > pla	7/16	1/16	2.7 (1.5–9.6)	0/16	0/16	ns
Capsaicin, 0.075% qid	Watson et al., 1993, 4	Parallel, 143	Caps > pla	44/74	21/69	3.4 (2.2–7.4)	18/74	2/69	4.7 (3.1–9.2)
Postmastectomy pain									
Capsaicin, 0.075% qid	[a]Watson and Evans, 1992, 3	Parallel, 25	Caps = pla	8/14	3/11	ns	1/14	0/11	ns
Post-surgical pain									
Capsaicin, 0.075% qid	Ellison et al., 1997, 4	Parallel, 99	Caps > pla	10/49	5/50	ns	4/49	4/50	ns
HIV-neuropathy									
Capsaicin, 0.075% qid	Paice et al., 2000, 3	Parallel, 26	Caps = pla	NA	NA	NA	0/15	0/11	ns
Mixed patients									
Capsaicin, 0.075% qid	McCleane, 2000, 4	Parallel, 74	Caps > pla	NA	NA	NA	0/33	0/41	ns
Glycine antagonist									
Mixed patients									
Glycine antagonist, 300 mg	[b]Wallace et al., 2002b, 4	Parallel, 63	Gly = pla	7/32	4/31	ns	1/32	2/31	ns

Combinations									
Painful polyneuropathy									
Gabapentin 3600 mg + venlafaxine 150 mg	Simpson, 2001, 2	Parallel, 11	Gab+ven> gab+pla	NA	NA	NA	NA	NA	NA
Mixed patients									
Gabapentin 2400 mg + morphine 60 mg	Gilron et al., 2005, 5	Cross-over, 41	Gab+mor>pla Gab+mor>gab Gab+mor>mor	32/41	13/42	2.1 (1.5–3.5)	6/47	1/44	ns

Pla = placebo, subl = sublingual, NA: dichotomized data are not available, ns: relative risk not significant.

[a] Additional data provided by author.
[b] Study include questionable neuropathic pain conditions.
[c] Data limited and difficult to interpret.
[d] 30 patients on multiple cross-over.
[e] 900 mg/day of gabapentin may be too low a dose for achieving an analgesic effect.
[f] Patients failing to respond to pre-study gabapentin excluded, which may cause an overestimation of the efficacy of pregabalin and gabapentin.
[g] For trigeminal neuralgia only.
[h] Partial cross-over.
[i] Add on therapy to carbamazepine or phenytoin.
[j] Pretreated with spinal cord stimulation, alternating drug/placebo administration, (NNT therefore not calculated).
[k] 200 mg/day of lamotrigine may be too low a dose for achieving an analgesic effect.
[l] Criteria for neuropathic pain inadequate.
[m] Methadone only superior in a dose of 20 mg.
[n] Mexiletine superior to placebo for highest dose.
[o] Patients with allodynia.
[p] Focal peripheral neuropathy, add-on therapy.
[q] Cannabinoid superior to placebo only 3 h after intake.
[r] Capsaicin on one leg and placebo on the other.
[s] No effect on steady pain.

strengthens the arguments for more head-to-head comparisons, and making such comparisons a regulatory requirement will help to make them happen.

Note added in proof

By September 2005, additional two large randomized trails have been published. Duloxetine had a significant pain relieving effect in painful diabetic neuropathy, with a NNT of 4.1 (2.9–7.2) for the highest doses of 60 and 120 mg/day (Goldstein et al., 2005). Pregabalin in flexible- or fixed-dose regimens had a significant pain relieving effect in postherpetic neuralgia and painful diabetic neuropathy with a NNT of 3.8 (2.6–7.3) (Freynhagen et al., 2005).

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.pain.2005.08.013

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EXHIBIT D

tions are not generally indicated unless features of serious conditions are identified.

- Management — Provide information, assurance and advice to resume normal activity and discuss other options for pain management as needed.
- Review — Reassess the pain and revise the management plan as required.

Interventions for Acute Musculoskeletal Pain

In addition to initial interventions such as providing information, assurance and advice to maintain reasonable activity levels, other options (non-pharmacological and pharmacological) exist for the management of acute musculoskeletal pain.

Non-pharmacological Interventions

Evidence for the effectiveness of a range of additional non-pharmacological (i.e. not involving medication) interventions for people with acute musculoskeletal pain is provided in the specific guideline topics. These include active, passive and behavioural therapies. Non-pharmacological interventions may be used in conjunction with pharmacological interventions (NHMRC 1999).

Key Message

Simple interventions (providing information, assurance and encouraging reasonable maintenance of activity) may be used alone or in combination with other interventions for the successful management of acute musculoskeletal pain. (CONSENSUS)

Pharmacological Interventions

Simple Analgesics (Non-Opioid)

Paracetamol is considered an effective medication for mild to moderate pain and can be used in conjunction with opioids to manage more severe pain.

Generally, paracetamol has few side effects. Paracetamol is contraindicated for people with liver dysfunction. It can be used when NSAIDs are contraindicated. Patients should be warned of the risk of liver damage with the combination of alcohol and paracetamol.

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

NSAIDs are considered effective in the management of mild to moderate pain. Concurrent use of opioids and NSAIDs may provide more effective analgesia than either of the drug classes alone. They may also reduce the side effects of opioid medications (NHMRC 1999).

The adverse effects of NSAIDs are potentially serious and all people cannot use them. NSAID use may result in gastro intestinal bleeding, renal dysfunction (particularly in older people), NSAID-induced asthma and impaired blood clotting. It is imperative that contraindications are identified and respected (e.g. asthma, peptic ulcer) (NHMRC 1999).

More recently, Cox-2 selective NSAIDs have become available. Evidence for their efficacy in a number of rheumatological disorders has been demonstrated. Currently they are not subsidised for acute musculoskeletal pain in Australia.

Key Messages

> Specific pharmacological interventions may be required to relieve pain; such agents can be used in conjunction with interventions. (CONSENSUS)

> Paracetamol or other simple analgesics administered regularly are recommended for relief of mild to moderate acute musculoskeletal pain. (CONSENSUS)

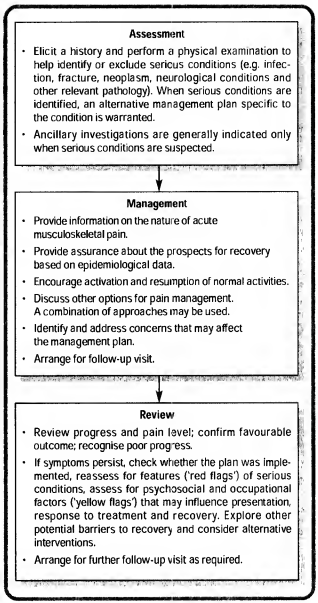

Figure 2.6
Management plan for acute musculoskeletal pain

> Where paracetamol is insufficient for pain relief, a non-steroidal anti-inflammatory (NSAID) medication may be used, unless contraindicated. (CONSENSUS)

Opioid Analgesics

Opioid analgesics bind to opioid receptors both within and outside the central nervous system and are used for management of severe pain.

All opioid medications have the potential to cause side effects including constipation, urinary retention, sedation, respiratory depression, nausea and vomiting. Titration of medication should occur to optimise the response to the analgesic and to minimise side effects. The following points are highlighted in the NHRMC (1999) acute pain guidelines:

- True allergy to opioids is uncommon; people may have side effects that are mistakenly referred to as 'allergies'.

- There is no evidence that the use of opioids for the treatment of severe acute pain leads to dependence on, or addiction to, opioid medications.
- The dosage should be tailored to each individual and the need for pain relief considered of greater importance than adhering strictly to a specific dose interval.

Key Message

Oral opioids may be necessary to relieve severe musculoskeletal pain. It is preferable to administer a short-acting agent at regular intervals, rather than on a pain-contingent basis. Ongoing need for opioid analgesia is an indication for reassessment. (CONSENSUS)

Muscle Relaxants

Muscle relaxants have the potential for side effects and show some short-term benefit in studies for low back pain. (Bigos et al. 1994; van Tulder et al. 1997).

Adjuvant Agents

There is no evidence to support the use of adjuvant agents, including antidepressants, anticonvulsants and oral corticosteroids, in the treatment of acute musculoskeletal pain.

Key Messages

> Any benefits from muscle relaxants may be outweighed by their adverse effects, therefore they cannot be routinely recommended. (CONSENSUS, LEVEL I)

> Adjuvant agents such as anticonvulsants and antidepressants are not recommended in the management of acute musculoskeletal pain. (CONSENSUS)

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